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(54) Title: 94 HUMAN SECRETED PROTEINS

(57) Abstract

The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human secreted proteins.

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94 Human Secreted Proteins

Field of the Invention

This invention relates to newly identified polynucleotides and the polypeptides encoded by these polynucleotides, uses of such polynucleotides and polypeptides, and their production.

Background of the Invention

Unlike bacterium, which exist as a single compartment surrounded by a membrane, human cells and other eucaryotes are subdivided by membranes into many functionally distinct compartments. Each membrane-bounded compartment, or organelle, contains different proteins essential for the function of the organelle. The cell uses "sorting signals," which are amino acid motifs located within the protein, to target proteins to particular cellular organelles.

One type of sorting signal, called a signal sequence, a signal peptide, or a leader sequence, directs a class of proteins to an organelle called the endoplasmic reticulum (ER). The ER separates the membrane-bounded proteins from all other types of proteins. Once localized to the ER, both groups of proteins can be further directed to another organelle called the Golgi apparatus. Here, the Golgi distributes the proteins to vesicles, including secretory vesicles, the cell membrane, lysosomes, and the other organelles.

Proteins targeted to the ER by a signal sequence can be released into the extracellular space as a secreted protein. For example, vesicles containing secreted proteins can fuse with the cell membrane and release their contents into the extracellular space - a process called exocytosis. Exocytosis can occur constitutively or after receipt of a triggering signal. In the latter case, the proteins are stored in secretory vesicles (or secretory granules) until exocytosis is triggered. Similarly, proteins residing on the cell membrane can also be secreted into the extracellular space by proteolytic cleavage of a "linker" holding the protein to the membrane.

Despite the great progress made in recent years, only a small number of genes encoding human secreted proteins have been identified. These secreted proteins include the commercially valuable human insulin, interferon, Factor VIII, human growth hormone, tissue plasminogen activator, and erythropoeitin. Thus, in light of

the pervasive role of secreted proteins in human physiology, a need exists for identifying and characterizing novel human secreted proteins and the genes that encode them. This knowledge will allow one to detect, to treat, and to prevent medical disorders by using secreted proteins or the genes that encode them.

Summary of the Invention

The present invention relates to novel polynucleotides and the encoded polypeptides. Moreover, the present invention relates to vectors, host cells, antibodies, and recombinant methods for producing the polypeptides and polynucleotides. Also provided are diagnostic methods for detecting disorders related to the polypeptides, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying binding partners of the polypeptides.

Detailed Description

Definitions

The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide.

In the present invention, a "secreted" protein refers to those proteins capable of being directed to the ER, secretory vesicles, or the extracellular space as a result of a signal sequence, as well as those proteins released into the extracellular space without necessarily containing a signal sequence. If the secreted protein is released into the extracellular space, the secreted protein can undergo extracellular processing to produce a "mature" protein. Release into the extracellular space can occur by many mechanisms, including exocytosis and proteolytic cleavage.

In specific embodiments, the polynucleotides of the invention are less than 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, or 7.5 kb in length. In a further embodiment, polynucleotides of the invention comprise at least 15 contiguous nucleotides of the coding sequence, but do not comprise all or a portion of any intron. In another embodiment, the nucleic acid comprising the coding sequence does not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the gene in the genome).

As used herein , a "polynucleotide" refers to a molecule having a nucleic acid sequence contained in SEQ ID NO:X or the cDNA contained within the clone deposited with the ATCC. For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, with or without the signal sequence, the secreted protein coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having the translated amino acid sequence generated from the polynucleotide as broadly defined.

In the present invention, the full length sequence identified as SEQ ID NO:X was often generated by overlapping sequences contained in multiple clones (contig analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X was deposited with the American Type Culture Collection ("ATCC"). As shown in Table 1, each clone is identified by a cDNA Clone ID (Identifier) and the ATCC Deposit Number. The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposit was made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for purposes of patent procedure.

A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained in SEQ ID NO:X, the complement thereof, or the cDNA within the clone deposited with the ATCC. "Stringent hybridization conditions" refers to an overnight incubation at 42° C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM sodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's

solution, 10% dextran sulfate, and 20 μg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65°C.

Also contemplated are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37°C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH_2PO_4; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 ug/ml salmon sperm blocking DNA; followed by washes at 50°C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

Of course, a polynucleotide which hybridizes only to polyA+ sequences (such as any 3' terminal polyA+ tract of a cDNA shown in the sequence listing), or to a complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone).

The polynucleotide of the present invention can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA

that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

The polypeptide of the present invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched , for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination.

(See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth Enzymol 182:626-646 (1990); Rattan et al., Ann NY Acad Sci 663:48-62 (1992).)

"SEQ ID NO:X" refers to a polynucleotide sequence while "SEQ ID NO:Y" refers to a polypeptide sequence, both sequences identified by an integer specified in Table 1.

"A polypeptide having biological activity" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention.)

Polynucleotides and Polypeptides of the Invention

FEATURES OF PROTEIN ENCODED BY GENE NO: 1

Preferred polypeptides of the invention comprise the following amino acid sequence: TRPEKVQAPLKWFKFQILDPP (SEQ ID NO:249). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in dendritic cells and to a lesser extent in other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune, nervous system, and inflammatory disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing

immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in dendritic cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, and autism. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Futhermore, expression of this gene product in primary dendritic cells also indicates that it may play a role in mediating responses to infection and controlling immunological responses, such as those that occur during immune surveillance. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:11 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 885 of SEQ ID NO:11, b is an integer of 15 to 899, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:11, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 2

The translation product of this gene share homology with the Tbc1 gene of Mus musculus which is thought to play a role in the cell cycle and differentiation of various tissues (See Genebank accession no. gi|988221 as well as Medline article no.96032578; all references available through these accessions are hereby incorporated by reference herein). One embodiment for this gene is the polypeptide fragments comprising the following amino acid sequence:

SAEFGVAPLPGRRGSPVRQLAQFRRRLLRGSGGRGAPGRPPRCPGEARVMXPPSCIQDEPFPHPLEPEP
GVSAQPGPGKPSDKRFRLWYVGGSCLDHRTTLPMLPWLMAEIRRRSQKPEAGGCGAPAAREVILVLSAP
FLRCVPAPGAGASGGTSPSATQPNPAVFIFEHKAQHISRFIHNSHDLTYFAYLIKAQPDDPESQMACHV
FRATDPSQVPDVISSIRQLSKXAMKEDAKPSKDNEDAFYNSQKFEVLYCGKVTVTPQEGPLKPHR
(SEQ ID NO:250); PMLPWLMAEIRRRS (SEQ ID NO:251); IHNSHDLTYFAYLIKAQPD
(SEQ ID NO:252); KFEVLYCGKVTV (SEQ ID NO:253); and/or ISSIRQLSKAMKE
(SEQ ID NO:254). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in smooth muscle and dendritic cells and to a lesser extent in other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cardiovascular diseases and immune and inflammatory disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and cardiovascular system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., smooth muscle and dendritic cells, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in smooth muscle and dendritic cells and homology to a protein involved in regulation of cell cycle and tissue differentiation indicates that polynucleotides and polypeptides corresponding to this gene are useful for the

detection/treatment and/or prevention of immune system disorders, cardiovascular disorders or diseases, including cancer and other proliferative disorders. The tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g., by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Alternatively, the protein is useful in the detection, treatment, and/or prevention of vascular conditions, which include, but are not limited to, microvascular disease, vascular leak syndrome, aneurysm, stroke, atherosclerosis, arteriosclerosis, or embolism. For example, this gene product may represent a soluble factor produced by smooth muscle that regulates the innervation of organs or regulates the survival of neighboring neurons. Likewise, it is involved in controlling the digestive process, and

such actions as peristalsis. Similarly, it is involved in controlling the vasculature in areas where smooth muscle surrounds the endothelium of blood vessels. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:12 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1126 of SEQ ID NO:12, b is an integer of 15 to 1140, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:12, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 3

The translation product of this gene shares sequence homology with alpha-1 antitrypsin (See Genebank accession no. gnl|PID|d1021080; all references available through this accession are hereby incorporated by reference herein). Alpha-1-antitrypsin is an important plasma protease inhibitor affecting a wide variety of serine proteases involved in coagulation, fibrinolysis and kinen generation.

Preferred polypeptides of the invention comprise the following amino acid sequence: GERRNWGGEVYYSTGYSSRK (SEQ ID NO:255). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in healing groin wound and to a lesser extent in some other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, wound healing disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the healing groin wound, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., healing, regenerative, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 132 as residues: Phe-25 to Tyr-30, Gln-37 to Arg-42, Lys-106 to Leu-112, Leu-123 to Leu-130, Gln-142 to Phe-150, Gln-183 to Lys-188, Asp-219 to Glu-226, Lys-359 to Glu-366. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in healing groin wound and homology to alpha-1 antitrypsin indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and therapeutic treatment of wound healing disorders. In addition, since healing wounds have transcriptional environments similar to developing tissues, The translation product of this gene is useful for the diagnosis and treatment of cancer and other proliferative disorders. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:13 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or

more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1431 of SEQ ID NO:13, b is an integer of 15 to 1445, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:13, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 4

The translation product of this gene shares homology with members of the HEMK family of modification methylases (See, e.g., Genbank Accession No. gb|AAD26417.1|AF131220_1; all references available through this accession are hereby incorporated by reference herein).

Preferred polypeptides of the invention comprise the following amino acid sequence: EPGAAQESW (SEQ ID NO:256); LCARPSCSYTGAENQGQPRSPGWGSSHVGWGWG VGSPFLGSQEWSGLAPDLPDQEEEQPVGRHSCPDMSQCIKRGHQPVGFSKHAWRCLVGCCPWEEEKRSC HPFGAXLLWVLRFALQPXVYEDPAALDGGEEGMDIXTHILALAPRLLKDSGSIFLEVDPRHPXLVSSWL QSRPDLYLNLVAVRRDFCGRPRFLHIRRSGP (SEQ ID NO:257); LCARPSCSYTGAENQGQPR SPGWGSSHVGWGWGVGSP (SEQ ID NO:258); FLGSQEWSGLAPDLPDQEEEQPVGRHSCPDMS QCIKR (SEQ ID NO:259); GHQPVGFSKHAWRCLVGCCPWEEEKRSCHPFGAXLLW (SEQ ID NO:260); VLRFALQPXVYEDPAALDGGEEGMDIXTHILALAPRL (SEQ ID NO:261); and/or LKDSGSIFLEVDPRHPXLVSSWLQSRPDLYLNLVAVRRDFCGRPRFLHIRRSGP (SEQ ID NO:262). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in immune and tumor tissues, and to a lesser extent in some other tissues such as heart.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and inflammatory disorders and tumorigenesis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and tumor tissues, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative

to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 133 as residues: Met-1 to Cys-6, Ser-26 to Gly-35. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in tumors of immune origins indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of such tumors, in addition to other tumors where expression has been indicated. Additionally, this gene is a good target for antagonists, particularly small molecules or antibodies, which block binding of the receptor by its cognate ligand(s). Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:14 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1194 of SEQ ID NO:14, b is an integer of 15 to 1208, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:14, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 5

The translation product of this gene shares sequence homology with mouse von Ebner minor salivary gland protein which may play a role in carbohydrate metabolism (See Genebank Accession No. gb|AAA87581.1|; all references available through this accession are hereby incorporated by reference herein).

Preferred polypeptides of the invention comprise the following amino acid sequence: QELLVKIPLDMVAGFNTPL (SEQ ID NO:263); LRIQLLHKLSFLVNALAK QVMNLLVP (SEQ ID NO:264); AGPWTFTLLCGLLAATLIQATLSPTAVLILGPKVIKEK LTQELKDHNATSILQQLPLL (SEQ ID NO:266); and/or HXIWLKVITXNILQLQVKPS (SEQ ID NO:265). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in respiratory tissues such as trachea, larynx and other pulmonary tissues, and to a lesser extent in other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, respiratory system and oral disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the respiratory tissues, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 134 as residues: Lys-39 to Asn-48, Arg-63 to Gly-68, Pro-101 to Gln-106. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution combined with the homology to von Ebner minor salivary gland protein indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of respiratory and oral diseases. Furthermore, The tissue distribution in pulmonary tissues also indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of tumors wihtin these tissues, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the

above listed tumors and tissues. Protein may show utility in the diagnosis, treatment, and/or prevention of disorders in carbohydrate metabolism.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:15 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1161 of SEQ ID NO:15, b is an integer of 15 to 1175, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:15, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 6

The gene encoding the disclosed cDNA is believed to reside on chromosome 2. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 2.

This gene is expressed primarily in fast-growing tissues such as fetal tissues, hematopoietic cells and tumor tissues and to a lesser extent in other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, growth disorders, tumorigenesis, and immune or inflammatory disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the fast-growing tissues such as fetal tissues, hematopoietic cells and tumor tissues, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a

disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in fast growing tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of cancer and other proliferative disorders. Expression in embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation or cellular division. Additionally, the expression in hematopoietic cells and tissues indicates that this protein may play a role in the proliferation, differentiation, and/or survival of hematopoietic cell lineages which implicates the protein product of this gene as being useful for the treatment and diagnosis of hematopoetic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. Thus, this gene is useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor cells.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:16 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2360 of SEQ ID NO:16, b is an integer of 15 to 2374, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:16, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 7

The translation product of this gene shares sequence homology with mitochondrial NADH-Ubiquinone oxidoreductase, chain 2.

Preferred polypeptides of the invention comprise the following amino acid sequence: HFIITLTTFFTNYFL (SEQ ID NO:267); and/or MKITFQDLFPMWNSFKCFL HGNVFSLFVLFPLLTCFSFPYTVNSGTKLDWVGWLVGWFFLEFMYINKGFEVTSENNISKRVLVRENIR IKSSPERVLRM (SEQ ID NO:268). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in stromal cells (cell code TF274), induced epithelial cells and human cerebellum.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, metabolic disorders and conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the liver, brain, and integument, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., lymph, bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in epithelial and cerebral tissues combined with the homology to a known mitochondrial NADH-Ubiquinone oxidoreductase gene indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, prevention, and/or treatment of various metabolic disorders such as Tay-Sach's disease, phenylkenonuria, galactosemia, porphyrias, and Hurler's syndrome. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional

supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:17 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1581 of SEQ ID NO:17, b is an integer of 15 to 1595, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:17, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 8

The translation product of this gene shares sequence homology with Platelet activating factor acetylhydrolase which inactivates Platelet activating factor, a potent phospholipid mediator affecting various physiological processes (See, e.g., Genbank Accession Nos. gi|349824|gb|AAA02880.1| and gi|2072303|gb|AAC04610.1|; all references available through this accession are hereby incorporated by reference herein).

Preferred polypeptides of the invention comprise the following amino acid sequence: RFWGSYEPHFSQEVSVIPP (SEQ ID NO:269); and/or IRGNYFSGRKKSSSDT PKGSKDKISVWNRSQXACIRICKVHPNYIQIYLWHSATSF (SEQ ID NO:270). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in CD34 depleted buffy coat (cord blood) and to a lesser extent in human prostate cancer, stage 3 fraction.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer, particularly of the prostate. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of

disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., prostate, cancerous and wounded tissues) or bodily fluids (e.g., lymph, cord blood, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in CD34 depleted buffy coat combined with the homology to Platelet-activating factor acetylhydrolases, proteins involved in regulation of platelet activity, indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in hematopoietic cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer e.g. by boosting immune responses.

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:18 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1273 of SEQ ID NO:18, b is an integer of 15 to 1287, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:18, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 9

Preferred polypeptides of the invention comprise the following amino acid sequence: AGNQVEPFHVSLPSCLSPLPHLGHSMGVPSPTAWPSLASFHTQKKARIRQEEES PPLPSPQELAFSALRVFFRV (SEQ ID NO:271). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in primary dendritic cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immunosuppression and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 138 as residues: Arg-20 to Lys-44, Arg-59 to Arg-68, Trp-74 to Lys-86, Thr-91 to Val-102. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in primary dendritic cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment

of a variety of immune system disorders. Expression of this gene product in dendritic cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer e.g. by boosting immune responses.

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:19 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1382 of SEQ ID NO:19, b is an integer of 15 to 1396, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:19, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 10

The translation product of this gene shares sequence homology with peptide/histidine transporter from Rattus norvegicus and other peptide transporters which are thought to be important in transporting amino acids and peptides into cells (See, e.g., Genbank Accession No. gb|AAD24570.1|AF121080_1; all references available through this accession are hereby incorporated by reference herein).

Preferred polypeptides of the invention comprise the following amino acid sequence: FIQQNISFLLGYSIPVGCVGLAFFIFLFATPVFITKPP (SEQ ID NO:272). Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome 11. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 11.

This gene is expressed primarily in macrophages and to a lesser extent in other immune cells including primary dendritic cells, neutrophils, resting T-cells, B cell lymphomas) and lung and fetal liver spleen.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer and disorders, particularly of the immune and hematopoietic systems. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and/or other tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 139 as residues: Arg-23 to Gln-30, Asp-37 to Asp-50, Glu-230 to Met-235, Pro-271 to Arg-281, Arg-306 to Ser-316, Ser-318 to Gly-325. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in macrophages and other immune cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of cancer and other proliferative disorders. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g., by boosting immune responses). Alternatively expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation or cellular division. Additionally, the expression in hematopoietic cells and tissues indicates that this protein may play a role in the proliferation, differentiation, and/or survival of hematopoietic cell lineages. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. In such an event, this gene is useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor cells. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiationm and could again be useful in cancer therapy. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:20 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1263 of SEQ ID NO:20, b is an

integer of 15 to 1277, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:20, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 11

The translation product of this gene shares sequence homology with procollagen-proline dioxygenase, an apparently secreted protein which is thought to be important in the formation of 4-hydroxyproline in collagens (See, e.g., Genbank Accession No. pir|A33832|DACHA; all references available through this accession are hereby incorporated by reference herein). Furthermore, the translation product has an EF-hand domain (Prosite PS00018) which is a calcium binding domain as found in calmodulin, calpain, spectrin alpha chain, etc., (See, e.g. GeneSeq Accession No.R78523; all references available through this accession are hereby incorporated by reference herein).

Preferred polypeptides of the invention comprise the following amino acid sequence:

VSAHHPSGADEGVTAXQILPTEEYEEAMSTMQVSQLDLFRLLDQNRDGHLQLREVLAQTRLGNGWWMTP
ESIQEMYAAIKADPDGDGVLSLQEFSNMDLRDFHKYMRSHKAESSELVRNSHHTWLYQGEGAHHIMRAI
RQRVLRLTRLSPEIVELSEPLQVVRYGEGGHYHAHVDSGPVYPETICSHTKLVANESVPFETSCRYMTV
LFYLNNVTGGGETVFPVADNRTYDEMSLIQDDVDLRDTRRHCDKGNLRVKPQQGTAVFWYNYLPDGQGW
VGDVDDYSLHGGCLVTRGTKWIANNWINVDPSRARQALFQQEMARLAREGGTDSQPEWALDRAXXDARV
EL (SEQ ID NO:273); AVFWYN (SEQ ID NO:274); TVLFYLNNVTGGGETVFP (SEQ
ID NO:275); DLFRLLDQNRDGHLQLREVLAQTRLGNGWWMTPESIQEMYAAIKADPDGDGVLS
LQEFS (SEQ ID NO:276); VSAHHPSGADEGVTAXQILPTEEYEEAMSTMQVSQLDL (SEQ ID
NO:277), FRLLDQNRDGHLQLREVLAQTRLGNGWWMTPESIQEMY (SEQ ID NO:278);
AAIKADPDGDGVLSLQEFSNMDLRDFHKYMRSHKAESS (SEQ ID NO:279); ELVRNSHHTWLY
QGEGAHHIMRAIRQRVLRLTRLSPEI (SEQ ID NO:280); VELSEPLQVVRYGEGGHYHAHVDS
GPVYPETICSHTKL (SEQ ID NO:281); VANESVPFETSCRYMTVLFYLNNVTGGGETVFPVA
DNR (SEQ ID NO:282); TYDEMSLIQDDVDLRDTRRHCDKGNLRVKPQQGTAVFW (SEQ ID
NO:283); YNYLPDGQGWVGDVDDYSLHGGCLVTRGTKWIANNWIN (SEQ ID NO:284);
and/or VDPSRARQALFQQEMARLAREGGTDSQPEWALDRAXXDARVEL (SEQ ID NO:285).
Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome 3. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 3.

This gene is expressed primarily in human endometrial tumor and to a lesser extent in brain, as well as a variety of other normal and cancerous tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, endometrial cancer, in addition to other proliferative disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive and neural systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, reproductive, and/or other tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid, lymph) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 140 as residues: Ser-21 to His-33, Ala-35 to Thr-43. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in endometrial tumors combined with the homology to procollagen-proline dioxygenase indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis, treatment and prevention of these tumors, in addition to other tumors where expression has been indicated. The polypeptides of the invention is a good target for antagonists, particularly small molecules or antibodies, which block binding of the receptor by its cognate ligand(s). Accordingly, preferred are antibodies and or small molecules which specifically bind an extracellular portion of The translation product of this gene. Also provided is a kit for detecting endometrial cancer. Such a kit comprises in one embodiment an antibody specific for The translation product of this gene bound to a solid support. Also provided is a method of detecting endometrial cancer in an individual which comprises a step of contacting an antibody specific for The translation product of this gene to a bodily fluid from the individual, preferably serum, and ascertaining

whether antibody binds to an antigen found in the bodily fluid. Preferably the antibody is bound to a solid support and the bodily fluid is serum. Additionally, the homology to a conserved collagen metabolizing protein would suggest that this protein may also be important in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias ie. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:21 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1767 of SEQ ID NO:21, b is an integer of 15 to 1781, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:21, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 12

This gene is expressed primarily in human osteoblastoma cell lines (5/23 unique sequences) and to a lesser extent in T cells (4/23).

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, osteoblastoma, and other bone-related disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing

immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skeletal system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., bone and/or other tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in tumors of bone origins indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. Additionally, this gene is a good target for antagonists, particularly small molecules or antibodies, which block binding of the receptor by its cognate ligand(s). Accordingly, preferred are antibodies and or small molecules which specifically bind an extracellular portion of The translation product of this gene. The extracellular regions can be ascertained from the information regarding the transmembrane domains as set out above. Also provided is a kit for detecting osteoblastoma and other bone related cancers. Such a kit comprises in one embodiment an antibody specific for The translation product of this gene bound to a solid support. Also provided is a method of detecting bone related cancers in an individual which comprises a step of contacting an antibody specific for The translation product of this gene to a bodily fluid from the individual, preferably serum, and ascertaining whether antibody binds to an antigen found in the bodily fluid. Preferably the antibody is bound to a solid support and the bodily fluid is serum. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:22 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1477 of SEQ ID NO:22, b is an integer of 15 to 1491, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:22, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 13

The translation product of this gene is a human homolog of the mouse acetylcholine receptor gamma chain, and is almost identitcal to a human acetylcholine receptor gamma chain (See, e.g., Genbank Accession Nos.: emb|CAA27442.1| and gb|AAA51568.1|; all references available through these accessions are hereby incorporated by reference herein) which is thought to be important in transmission of nerve impulses to muscles.

Preferred polypeptides of the invention comprise the following amino acid sequence: LLADLMRNYDPHLRP (SEQ ID NO:286); ISVTYFPFDWQNCSLIFQS (SEQ ID NO:287); SMARGVRKVFLRLLPQ (SEQ ID NO:288); QASPAIQACVDACNLMAR (SEQ ID NO:289); and/or YNQVPDLPFPGDPRPYL (SEQ ID NO:290). Polynucleotides encoding these polypeptides are also provided. This gene maps to chromosome 2, and therefore, is used as a marker in linkage analysis for chromosome 2. Included in this invention as preferred domains are Neurotransmitter-gated ion-channels domains, which were identified using the ProSite analysis tool. Structurally, members of the family of Neurotransmitter-gated ion-channels are composed of a large extracellular glycosylated N-terminal ligand-binding domain,followed by three hydrophobic transmembrane regions which form the ionic channel, followed by an intracellular region of variable length. A fourth hydrophobic region is found at the C-terminal of the sequence. In the N-terminal extracellular domain of AchR/GABA/5HT3/Gly receptors, there are two conserved cysteine residues, which, in AchR, have been shown to form a disulfide bond essential to the tertiary structure of the receptor. A number of amino acids between the two disulfide-bonded cysteines are also conserved. We have therefore used this region as a signature pattern for this subclass

of proteins. The concensus pattern is as follows: C-x-[LIVMFQ]-x-[LIVMF]-x(2)-[FY]-P-x-D-x(3)-C.

Preferred polypeptides of the invention comprise the following amino acid sequence: CSISVTYFPFDWQNC (SEQ ID NO:291). Polynucleotides encoding these polypeptides are also provided. Further preferred are polypeptides comprising the Neurotransmitter-gated ion-channel domain of the amino acid sequence referenced in Table 1 for this gene, and at least 5, 10, 15, 20, 25, 30, 50, or 75 additional contiguous amino acid residues of the amino acid sequence referenced in Table 1 for this gene . The additional contiguous amino acid residues is N-terminal or C-terminal to the Neurotransmitter-gated ion-channel domain. Alternatively, the additional contiguous amino acid residues is both N-terminal and C-terminal to the Neurotransmitter-gated ion-channel domain, wherein the total N- and C-terminal contiguous amino acid residues equal the specified number. The above preferred polypeptide domain is characteristic of a signature specific to Neurotransmitter-gated ion-channels.

This gene is expressed primarily in fetal tissues (56/58 unique sequences), specifically lung (42/58) and Dura Mater (14/58). It was also detected (1 sequence each) in a differentially expressed human cerebellum library and human tonsil library

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly fetal lung and brain, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues and cell types (e.g., developmental, neural, differentiating, and/or other tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid, pulmonary surfactant) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 142 as residues: Met-1 to Pro-7, Gln-21 to Glu-27,

Arg-35 to Asp-49, Asn-66 to Leu-72, Trp-82 to Glu-95, Pro-158 to Asn-163. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in dura mater combined with the homology to a conserved acetylcholine receptor indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses , autism, and altered bahaviors, including disorders in feeding, sleep patterns, balance, and preception. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, and/or disorders of the cardiovascular and pulmonary systems. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:23 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1825 of SEQ ID NO:23, b is an integer of 15 to 1839, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:23, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 14

Preferred polypeptides of the invention comprise the following amino acid sequence: VLKYALFLVLKNYYYCPY (SEQ ID NO:292). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in small intestine and to a lesser extent in lung cancer.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, gastrointestinal and pulmonary disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the intestinal and pulmonary systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., gastrointestinal, pulmonary, and/or other tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid, lymph, and/or pulmpnary surfactant) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in small intestine indicates a role in the detection and/or treatment of gastro-intestinal disorders including Whipple's disease, Ulcers, and indigestion. Expression in the lung indicates a potential role in the treatment and/or detection of certain pulmonary defects such as pulmonary edema and embolism, bronchitis, cystic fibrosis and lung cancer. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:24 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1370 of SEQ ID NO:24, b is an integer of 15 to 1384, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:24, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 15

In another embodiment, polypeptides of the invention comprise the following amino acid sequence:

MREYGVERDLAVYNQLLNIFPKEVFRPRNIIQRIFVHYPRQQECGIAVLEQMENHGVMPNKETEFLLIQ
IFGRKSYPMLKLVRLKLWFPRFMNVNPFPVPRDLPQDPVELAMFGLRHMEPDLSARVTIYQVPLPKDST
GAADPPQPHIVGIQSPDQQAALARHNPARPVFVEGPFSLWLRNKCVYYHILRADLLPPEEREVEETPEE
WNLYYPMQLDLEYVRSGWDNYEFDINEVEEGPVFAMCMAGAHDQATMAKWIQGLQETNPTLAQIPVVFR
LAGSTRELQTSSAGLEEPPLPEDHQEEDDNLQRQQQGQS (SEQ ID NO:293).

Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in brain and to a lesser extent in pancreas, testes, and other tissue types.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological, behavioral, gastrointestinal, and endocrine disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., brain, endocrine, and/or other tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid, and lymph) or another tissue or cell sample taken from an individual having such a

disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 144 as residues: Val-33 to Arg-39, Ser-57 to Thr-66, Pro-80 to Lys-86, Pro-155 to Cys-160, Val-215 to Pro-223, Pro-250 to Gly-255, Pro-311 to Glu-323, Arg-338 to Tyr-344, Ser-396 to Gln-401, Pro-410 to Ser-431. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in brain indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:25 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1667 of SEQ ID NO:25, b is an integer of 15 to 1681, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:25, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 16

The translation product of this gene shares sequence homology with the acid labile subunit of the insulin like growth factor binding subunit which is thought to be important in modulating the activity of Insulin like growth factor. In addition, this gene also shares homology with the melibiose carrier protein (thiomethylgalactoside permease II) of Caenorhabditis elegans (See Genebank Accession No. gi|1280135; all references available through this accession are hereby incorporated by reference herein).

Preferred polypeptides of the invention comprise the following amino acid sequence: FQFGWASTQISHLSLIPEL (SEQ ID NO:294); LRYAFTVVANITVY (SEQ ID NO:295); FVYGSMSFLDKVANGLA (SEQ ID NO:296); WHLVGTVCVLLSFPFIF (SEQ ID NO:297); and/or GHFLNDLCASMWFTY (SEQ ID NO:298). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in macrophages and to a lesser extent in dendritic cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and hematopoeitic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoetic and/or immune systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g.hematopoeitic, immune, and/or other tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid, and lymph) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 145 as residues: Ala-28 to Ala-33, Arg-38 to Leu-48, Thr-120 to Lys-125, Gly-155 to Gln-163, Gly-200 to Glu-214. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution predominantly in dendritic cells and macrophages combined with homology to a growth factor binding subunit indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:26 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1935 of SEQ ID NO:26, b is an integer of 15 to 1949, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:26, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 17

The translation product of this gene was shown to have homology to the T13C5.6 gene product from Caenorhabditis elegans (See Genebank Accession No. gi|1049369; all references available through this accession are hereby incorporated by reference herein).

Preferred polypeptides of the invention comprise the following amino acid sequence: AIPLRVLVVLWAFVLGLSRVMLGRHNVTDVAFGFFLGYMQ (SEQ ID NO:299); and/or VGLSRVLGRHTDV (SEQ ID NO:300). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in placenta and small intestine.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, pregnancy, reproductive, and/or gastrointestinal disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the intestinal and endocrine systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, gastrointestinal, and/or other tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid, amniotic fluid,) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in placenta indicates a potential role for this protein in the detection and/or treatment of pregnancy disorders such as miscarriage and/or gastro-intestinal disorders such as indigestion, ulcers and Whipple's disease. Alternatively, polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, prevention, and/or treatment of various metabolic disorders such as Tay-Sachs disease, phenylkenonuria, galactosemia, porphyrias, and Hurler's syndrome. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional

supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:27 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2272 of SEQ ID NO:27, b is an integer of 15 to 2286, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:27, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 18

Preferred polypeptides of the invention comprise the following amino acid sequence: SFYKMKRNSYDRLRKVV (SEQ ID NO:301). Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1.

This gene is expressed primarily in prostate and spleen and to a lesser extent in most cell types.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, prostate and immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and endocrine systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, immune, and/or other tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid, seminal fluid,

and lymph) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in prostate indicates a potential role in the treatment and/or detection of prostate disorders including benign prostate hyperplasia and prostate cancer. Expression in spleen indicates a role in the treatment and/or detection of spleen disorders such as splenitis and spleen cancer. Alternatively, the expression in the spleen may suggest that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Expression of this gene product in tonsils indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer e.g. by boosting immune responses.

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:28 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 516 of SEQ ID NO:28, b is an integer of 15 to 530, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:28, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 19

This gene was shown to have homology to both a human IgE-binding protein as well as to the human gene for Human Factor XIII (See Genebank Accession Nos. gb|S76337|S76337 and Q25893, respectively).

Preferred polypeptides of the invention comprise the following amino acid sequence: LHQLRPPHRFPLIPPAAAEGAGAPPGCGYCVFWLLNPLP (SEQ ID NO:302), and/or MPWKRAVVLLMLWFIGQAMWLAPAYVLEFQGKNTFLFIWLAGLFFLLINCSILIQIISH YKEEPLTERIKYD (SEQ ID NO:303). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in infant brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological and behavioural disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, immune, and/or other tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid, and lymph) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in infant brain indicates that polynucleotides and polypeptides corresponding to this gene are useful for detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses , autism, and altered bahaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. Alternatively, considering the homology to a conserved human gene for IgE as well as to a conserved blood clotting factor may suggest this gene is useful for the diagnosis and treatment of a variety of immune system disorders. Homology of this gene to a blood clotting factor, specifically, indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer e.g., by boosting immune responses.

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia.Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. In addition, this gene product may have commercial utility in the expansion of

stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:29 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1282 of SEQ ID NO:29, b is an integer of 15 to 1296, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:29, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 20

Preferred polypeptides of the invention comprise the following amino acid sequence: ARAQPFAFQLRPAPGRPGSPVA (SEQ ID NO:304); AGLPGALTAPAXHHHADSRPAELVVQPLSPPRPLLSHAGLASAAGASSLXRVPGEAESLCALSPGSALR FPAASCSRPXREPSGDEGTAGALPSPWLAALGPGGRPAVRRVLPRLGGRAGQLPRGLPVPRGLRHAGRY HLLRLLRAPLLLRRGRRQAGAGRLHQRPPRTGAPRHHCAACLRPLSHRRLHLHCVHHPGLCSGYLLLHL FETQGALAAANPLLTPQLSDRDPAHDPDLHQPQGTLPAVQHSHELQLHRRLHPQVLLSHLVSWCHPSI SLTPFSRSPHWLGRAVQTFSSX (SEQ ID NO:305); AGLPGALTAPAXHHHADSRPAELVVQP LSPPRPLLSHA (SEQ ID NO:306); GLASAAGASSLXRVPGEAESLCALSPGSALRFPAASCSRP (SEQ ID NO:307); XREPSGDEGTAGALPSPWLAALGPGGRPAVRRVLPRLGGR (SEQ ID NO:308); AGQLPRGLPVPRGLRHAGRYHLLRLLRAPLLLRRGRRQAG (SEQ ID NO:309); AGRLHQRPPRTGAPRHHCAACLRPLSHRRLHLHCVHHPGL (SEQ ID NO:310); CSGYLLLHLF ETQGALAAANPLLTPQLSDRDPAHDPDLHQ (SEQ ID NO:311); and/or PQGTLPAVQHSH ELQLHRRLHPQVLLSHLVSWCHPSISLTPFSRSPHWLGRAVQTFSSX (SEQ ID NO:312). Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome 4. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 4.

This gene is expressed primarily in heart and to a lesser extent in the embryo.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a

biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cardiovascular and developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cardiovascular and developmental systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., cardiopulmonary, developmental, and/or other tissues) or bodily fluids (e.g., lymph, sputum, serum, plasma, urine, synovial fluid and spinal fluid, amniotic fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 149 as residues: Gln-23 to Gly-30, Gln-35 to Gln-43, Leu-73 to Glu-84, Arg-125 to Pro-133, Ser-140 to Thr-145, Thr-153 to Thr-164. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in heart indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or detection of a range of vascular conditions, which include, but are not limited to, microvascular disease, vascular leak syndrome, aneurysm, stroke, atherosclerosis, arteriosclerosis, embolism, vasculitis, myocardial infarction, myocarditis, ischemia, stroke, in addition to developmental and metabolic disorders. For example, this gene product may represent a soluble factor produced by smooth muscle that regulates the innervation of organs or regulates the survival of neighboring neurons. Likewise, it is involved in controlling the digestive process, and such actions as peristalsis. Similarly, it is involved in controlling the vasculature in areas where smooth muscle surrounds the endothelium of blood vessels. Alternatively, the expression in embryonic tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of cancer and other proliferative disorders. Furthermore, protein may play a role in the regulation of cellular division. In such an event, this gene is useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early

hematopoietic stem and committed progenitor cells. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:30 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1965 of SEQ ID NO:30, b is an integer of 15 to 1979, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:30, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 21

This gene is expressed primarily in human teratocarcinoma cell line treated with retinoic acid and human brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental abnormalties and neural disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., developing, differentiating, neural, and/or other

tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid, amniotic fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in teratocarcinoma cell line indicates that polynucleotides and polypeptides corresponding to this gene are useful for early diagnosis and treatment of develpmental abnormalities, including agenesis, aplasia, hypoplasia, dysraphic anormalities, division failures, dysplasia, etc. Additionally, the gene and its expression can be used for teratogen detection or classification. Alternatively, considering the expression within human brain tissue may suggest that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:31 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1260 of SEQ ID NO:31, b is an

integer of 15 to 1274, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:31, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 22

The translation product of this gene was shown to have homology to the human B-cell growth factor which is known to be involved in the maturation of B-cells (See Genebank Accession No. gi|522145; all references available through this accession are hereby incorporated by reference herein).

Preferred polypeptides of the invention comprise the following amino acid sequence: VAHTCNLSTLGGQGGRIERTAGQEFKTS (SEQ ID NO:313). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in multiple sclerosis and prostate tissues and to a lesser extent in brain and osteoblasts.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, muscle, reproductive, and neural disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system and/or PNS, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., muscle, reproductive, and/or other tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid, seminal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 151 as residues: Gln-28 to Asp-35. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in multiple sclerosis indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory

conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:32 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1517 of SEQ ID NO:32, b is an integer of 15 to 1531, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:32, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 23

The translation product of this gene was shown to have homology to the B0035.14 gene of Caenorhabditis elegans (See, e.g., Genbank Accession No. gnl|PID|e242592; all references available through this accession are hereby incorporated by reference herein).

Preferred polypeptides of the invention comprise the following amino acid sequence: TIKMQTENLGVVYYVNKDF (SEQ ID NO:314); MVSNPPY (SEQ ID NO:316); HASEL (SEQ ID NO:317); and/or VEEDYVTNIRNNC (SEQ ID NO:315). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in bone marrow and to a lesser extent in lung and various tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic, and/or cardiopulmonary disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., proliferating, haematopoeitic, and/or other tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid, pulmonary surfactant) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 152 as residues: Ile-34 to Glu-39, Lys-49 to Lys-56, Val-63 to Glu-68, Thr-73 to Asp-88, Arg-97 to Pro-107. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in bone marrow indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or

chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency, etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:33 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2076 of SEQ ID NO:33, b is an integer of 15 to 2090, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:33, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 24

Preferred polypeptides of the invention comprise the following amino acid sequence: LVALDRMEYVRTFRKREDLRGRLFWVALDLLDLLD (SEQ ID NO:318). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in T-cells and breast cancer tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders and breast cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of

disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, breast, proliferating, and/or other tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid, breast milk, and lymph) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 153 as residues: Tyr-105 to Pro-113, Gln-122 to Pro-133, Pro-140 to Asp-155. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in T cells and breast cancer indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product in T-cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer e.g., by boosting immune responses.

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the

differentiation and/or proliferation of various cell types. The expression of the gene in the breast cancer tissue may indicate T-cell mediated immune reaction to the cancer tissue.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:34 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 992 of SEQ ID NO:34, b is an integer of 15 to 1006, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:34, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 25

The translation product of this gene shares sequence homology with an yeast ankyrin repeat-containing protein Akr1p which is thought to be important in pheromone response pathway (See Genebank Accession No. gi|466522; all references available through this accession are hereby incorporated by reference herein).

Preferred polypeptides of the invention comprise the following amino acid sequence: SVALFYNFGKSWKSDPGIIKXTEEQKKKTIVELAETGSLDLSIFCSTCLIRKPVRSK HCGVCNRCIAKFDHHCPWVGNCVGAGNHRYF (SEQ ID NO:319); FDHHCPWVGNCV (SEQ ID NO:320); and/or QMYQISCLGITTNERMNARR (SEQ ID NO:321). Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome 12. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 12.

This gene is expressed primarily in human lung cancer cells, B-cell lymphoma and to a lesser extent in fetal tissues and tumor cells of various origins.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, cancer of various origins, particularly of the lungs and hematopoietic systems. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the lung, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., lung, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid, pulmonary surfactant, and lymph) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 154 as residues: Thr-28 to Phe-35, Asp-140 to Ser-145. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in lung cancer indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product in lymphomas indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer e.g., by boosting immune responses.

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Alternatively, distribution

in tumor tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of cancers of various origins, especially lung B-cell lymphoa, stomach cancer, osteoclastoma. Additionally, this gene is a good target for antagonists, particularly small molecules or antibodies, which block binding of the receptor by its cognate ligand(s). Accordingly, preferred are antibodies and or small molecules which specifically bind an extracellular portion of The translation product of this gene. Also provided is a kit for detecting lung cancer. Such a kit comprises in one embodiment an antibody specific for The translation product of this gene bound to a solid support. Also provided is a method of detecting lung cancer in an individual which comprises a step of contacting an antibody specific for The translation product of this gene to a bodily fluid from the individual, preferably serum, and ascertaining whether antibody binds to an antigen found in the bodily fluid. Preferably the antibody is bound to a solid support and the bodily fluid is serum. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:35 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1773 of SEQ ID NO:35, b is an integer of 15 to 1787, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:35, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 26

The gene encoding the disclosed cDNA is believed to reside on chromosome 15. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 15.

This gene is expressed primarily in infant brain and to a lesser extent in a variety of other tissues and cell types.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental and neurodegenerative diseases of the brain and nervous system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, CNS, and/or PNS, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., developmental, differentiating, neural, and/or other tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 155 as residues: Ser-33 to Ile-41. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in infant brain indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia,

mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:36 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1187 of SEQ ID NO:36, b is an integer of 15 to 1201, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:36, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 27

The translation product of this gene shares sequence homology with a zinc transporter, ZnT-1, which is thought to regulate zinc excretion from cells and maintain homeostasis (See Genebank Accession No. gb|AAA79234.1|, all references available through this accession are hereby incorporated by reference herein; as well as Palmiter and Findley, EMBO J. 14:639-649 (1995), which is hereby incorporated by reference herein). Transformation of normal cells with a mutant rat ZnT-1 lacking the first membrane-spanning domain conferred zinc sensitivity on wild-type cells, suggesting that ZnT-1 functions as a multimer. Deletion of the first two membrane-

spanning domains resulted in a non-functional molecule, whereas deletion of the C-terminal tail produced a toxic phenotype. Transmembrane domains of the protein of the current invention are predicted using PSORT to comprise the following amino acid residues of the amino acid sequence referenced in Table 1 for this gene: Ser-42 to Ala-58, Ala-83 to Leu-99, Leu-115 to Gly-131, Val-249 to Val-265, and/or Val-314 to Leu-330. Therefore, preferred polypeptides of the present invention are the predicted extracellular domains, comprising the following amino acid sequence: RVTSSLAMLSDS (SEQ ID NO:322); AIERFIEPHEMQQPL (SEQ ID NO:323); and/or NALVFYFSWKGCSEGDFCVNPCFPDPCKPFVEIINSTHASVYEAGPCWV (SEQ ID NO:324). An additional preferred polypeptide fragment of the invention comprises the following amino acid sequence: AGIRHERNRGRLLCMLALTFMFMVLEVVVSR VTSSLAMLSDSFHMLSDVLALVVALVAERFARRTHATQKNTFGWIRAEVMGALVNAIFLTGLCFAILLE AIERFIEPHEMQQPLVVLGVGVAGLLVNVLGLCLFHHHSGFSQDSGHXHSHGGHGHGHGLPKGPRVKST RPGSSDINVAPGEQGPDQEETNTLVANTSNSNGLKLDPADPENPRSGDTVEVQVNGNLVREPDHMELEE DRAGQLNMRGVFLHVLGDALGSVIVVVNALVFYFSWKGCSEGDFCVNPCFPDPCKAFVEILIVLMHQFM (SEQ ID NO:325). Polynucleotides encoding this sequence are also provided.

This gene is expressed primarily in colon, lung, liver, lymphoma, osteosarcoma, adrenal gland tumor and fibroblasts.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative disorders, as well as gastrointestinal disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, gastrointestinal, and/or other tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 156 as residues: Arg-50 to Thr-58, Ser-125 to Gly-132. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution and homology to ZnT-1 indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of disorders associated with the regulation of zinc homeostasis. Although zinc is an important trace element in many biological systems, several lines of evidence suggest that this transporter may serve as a point of intervention particularly in the treatment of neurological diseases. The metabolism of zinc in the brain has been shown to be regulated by a number of transport proteins, including ZnT-1. Pharmacological doses of zinc cause neuronal death, and some estimates indicate that extracellular concentrations of zinc could reach neurotoxic levels under pathological conditions. In Alzheimer's disease, zinc has been shown to aggregate beta-amyloid, a form which is potentially neurotoxic. The zinc-dependent transcription factors NF-kappa B and Sp1 bind to the promoter region of the amyloid precursor protein (APP) gene. Zinc also inhibits enzymes which degrade APP to nonamyloidogenic peptides and which degrade the soluble form of beta-amyloid. The changes in zinc metabolism which occur during oxidative stress is important in neurological diseases where oxidative stress is implicated, such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS). Zinc is a structural component of superoxide dismutase 1, mutations of which give rise to one form of familiar ALS. After HIV infection, zinc deficiency is found which is secondary to immune-induced cytokine synthesis. Zinc is involved in the replication of the HIV virus at a number of sites. Collectively, this transporter may prove useful in the treatment and diagnosis of several disorders related to zinc regulation. Alternatively, the tissue distribution within lymphomas indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in immune tissue indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or

other processes that may also suggest a usefulness in the treatment of cancer e.g. by boosting immune responses.

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:37 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1882 of SEQ ID NO:37, b is an integer of 15 to 1896, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:37, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 28

The translation product of this gene was shown to have homology to the mouse interferon-stimulated gene 15 and human calnexin (See Genbank Accession Nos. gb|AAB02697.1| and gi|306481|gb|AAA21013.1|; all references available through these accessions are hereby incorporated by reference herein) which may implicate this gene as playing a role in regulation of proliferating and differentiating cells.

Preferred polypeptides comprise the following amino acid sequence: MFTFASMTKEDSKLIALIWPSEWQMIQKLFVVDHVIKITRIEVGDVNPSETQYISEPKLCPECREGLLC QQQRDLREYTQATIYVHKVVDNKKVMKDSAPELNVSSSETEEDKEEAKPDGEKDPDFNQSXGGTKRQKI SHQNYIAYQKQVIRRSMRHRKVRGEKALLVSANQTLKELKIQIMHAFSVAPFDQNLSIDGKILSDDCAT LGTLGVIPESVILLKADEPIADYAAMDDVMQVCMPEEGFKGTGLLGH (SEQ ID NO:326); SAPELNVSSSETEEDKEEAKP (SEQ ID NO:327); FQDKNRPCLSNWPEDTDVLYIVSQFFVEEWRKFVRKPTRCSPVSSVGNSALLCPHGGL (SEQ ID NO:329); MFTFASMTKEDSKLIALIWPSEWQMIQKLFVVDHVIKITRIE (SEQ ID NO:330); VGDVNPSETQYISEPKLCPECREGLLCQQQRDLREYTQATIY (SEQ ID NO:331); VHKVVDNK KVMKDSAPELNVSSSETEEDKEEAKPDGEKDPDF (SEQ ID NO:332); NQSXGGTKRQKISHQN YIAYQKQVIRRSMRHRKVRGEKALLV (SEQ ID NO:333); SANQTLKELKIQIMHAFSVAPFDQ NLSIDGKILSDDCATLGT (SEQ ID NO:334); LGVIPESVILLKADEPIADYAAMDDVMQVCM PEEGFKGTGLLGH (SEQ ID NO:335); and/or KELKIQIMHAFSVAPFDQ (SEQ ID NO:328). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in brain and hematological tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancers, developmental and regulatory diseases of the brain and immune system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain and immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 157 as residues: His-26 to Phe-31. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in brain indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of

neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, expression in T-cells and bone marrow, and homology to the mouse interferon-stimulated gene 15 and human calnexin proteins indicate that the protein product of this gene might also be useful for the diagnosis and treatment of immune disorders including: leukemias, lymphomas, auto-immunities, immunodeficiencies (e.g., AIDS), immuno-supressive conditions (transplantation) and hematopoeitic disorders. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of general microbial infection, inflammation, and cancer (e.g., by boosting immune responses). Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:38 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1138 of SEQ ID NO:38, b is an

integer of 15 to 1152, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:38, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 29

Preferred polypeptides of the invention comprise the following amino acid sequence: RGERSEELLGREGLSGSQ (SEQ ID NO:336), and/or AEAAEGEKGVRSCWAER DCPAPRCWASWGAQPSWDGSQVLLWRSCCCCCCWPPAFSTDGRTVTWRGTVQLQGETESAGPSLGPSGG GATWESFTITVILATYLMCRMWASTTTTTPATXLTTXTTTTTPTATIPATLAEAAVAGACGQQLPLPSH LFPGQVDPMFPCGRMHLWGERXEQ (SEQ ID NO:337). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in placenta.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental anomalies or fetal deficiencies. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing fetus, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, and/or other tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid, amniotic fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 158 as residues: Gly-35 to Asp-40, Asn-51 to Trp-59. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in placenta indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of developmental anomalies or fetal deficiencies, reproductive dysfunction, as well as ovarian and other endometrial cancers. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate

ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:39 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1003 of SEQ ID NO:39, b is an integer of 15 to 1017, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:39, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 30

The translation product of this gene shares sequence homology with ALS (Acid Labile Subunit of Insulin-Like Growth Factor) which is thought to be important in the regulation of IGF availibility. As such, it is likely that the product of this gene is involved in the regulation of various proliferation-dependent cellular processes that is attributable to cancer progression (See Genbank Accession No. gi|184808; all references available through this accession are hereby incorporated by reference herein).

Preferred polypeptides of the invention comprise the following amino acid sequence: FHGLGRLHTVHL (SEQ ID NO:338), AAFTGLALLEQLDLSDNAQLR (SEQ ID NO:339), HEVPDAPRPTPT (SEQ ID NO:341), and/or AFRGLHSLD (SEQ ID NO:340). Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome 22. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 22.

This gene is expressed primarily in cerebellum.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative diseases, growth deficiencies, osteoporosis, catabolic disorders and diabetes. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system and other periferial tissues, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, proliferating, and/or other tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 159 as residues: Thr-41 to Gly-47, Pro-170 to Asp-176, Leu-257 to Trp-262, Gln-276 to Ser-283, Arg-323 to Leu-330, Pro-362 to Val-374. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution cerebellum and homology to ALS (Acid Labile Subunit of Insulin-Like Growth Factor) indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of a variety of metabolic disorders, growth deficiencies, osteoporosis, catabolic disorders (including AIDS) and diabetes. Nearly all of the insulin-like growth factor (IGF) in the circulation is bound in a heterotrimeric complex composed of IGF, IGF-binding protein-3, and the acid-labile subunit (ALS). The protein product of this gene therefore may afford the ability to potentiate the biological actions of IGF or similar growth factors and cytokines. Studies which demonstrate the beneficial effect of IGF-I in amyotrophic lateral-sclerosis, would suggest a role in this disease as well. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement.

Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:40 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1763 of SEQ ID NO:40, b is an integer of 15 to 1777, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:40, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 31

The translation product of this gene was shown to have homology to diacylglycerol kinase which is known to be important in lipid metabolism (See Genebank Accession No.gi|1939; all references available through this accession are hereby incorporated by reference herein).

Preferred polypeptides of the invention comprise the following amino acid sequence: MVVADRNRASSSSYLCLLLFSLSLFLCHETVCDRATCLFFFLKFFFLFMCRCMSW GFKNFKAGLLMQSMPTSGILRERKRLHVVRIPQGTEKKLETVEMQI (SEQ ID NO:342), and/or IPQGTEKKLETV (SEQ ID NO:343). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental and neurodegenerative diseases of the brain and nervous system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, expression of this gene at significantly higher or lower levels

is routinely detected in certain tissues or cell types (e.g., neural, and/or other tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 160 as residues: Gly-49 to Ser-54, Lys-61 to Arg-68. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in brain combined with the homology to a known enzyme involved in lipid metabolism indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In particular, this gene may have utility in the diagnosis, treatment, and/or prevention of disorders involving the PNS, CNS and/or other tissues which rely on lipid-containing structures such as myelin sheath dependent nerves. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:41 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 989 of SEQ ID NO:41, b is an integer of 15 to 1003, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:41, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 32

This gene is expressed primarily in amygdala.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental and neurodegenerative diseases of the brain and nervous system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 161 as residues: Met-1 to Lys-6. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in amygdala indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection,

treatment, and/or prevention of aphasia, depression, schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's disease, specific brain tumors, mania, dementia, paranoia, addictive behavior and sleep disorders. The amygdala processes sensory information and relays this to other areas of the brain including the endocrine and autonomic domains of the hypothalamus and the brain stem. As such, The translation product of this gene may show commercial utility in the diagnosis, treatment, and/or prevention of various endocrine, cardiovascular, and pulmonary disorders, particularly those disorders directly associated with CNS/autonomic control. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:42 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1187 of SEQ ID NO:42, b is an integer of 15 to 1201, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:42, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 33

The gene encoding the disclosed cDNA is believed to reside on chromosome 9. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 9.

Preferred polypeptides of the invention comprise the following amino acid sequence: NPRLPLPRGGSLRLLSSPANSNNAKAYPFSRFPSPIF (SEQ ID NO:344). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in B-cell lymphoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, haemopoietic and immune diseases and/or disorders including cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the haemopoietic and immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in B-cell lymphoma indicates polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and

graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:43 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1162 of SEQ ID NO:43, b is an integer of 15 to 1176, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:43, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 34

This gene is expressed primarily in breast cancer.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders of the reproductive organs and cancer, particularly of the mammary glands. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, breast, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell

sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 163 as residues: Asp-77 to Gly-127. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in tumors of breast origins indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of such tumors, in addition to other tumors. Representative uses are described in the "Hyperproliferative Disorders", "Infectious Disease", and "Binding Activity" sections below, in Example 11, and 27, and elsewhere herein. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:44 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 555 of SEQ ID NO:44, b is an integer of 15 to 569, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:44, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 35

Preferred polypeptides encoded by this gene comprise the following amino acid sequence: MVQEAPALVRLSLGSHRVKGPLPVLKLQPEGWSPSTLWSCASVWKDSC (SEQ ID NO:345), and/or ALASSLVAENQGFVAALMVQEAPALVRLSLGSHRVKGPLPVLKLQPEGWSPST

LWSCASVWKDSCMHPWRLSMCPACVLAALPALCSCLCSPDARPPHGWMSMPFTPHPLVSRAMPTCHPCS (SEQ ID NO:346). Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome 11. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 11.

This gene is expressed primarily in placenta, dendritic cells, brain, and to a lesser extent in infant cells and tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders of developing cells and tissues, particularly growth disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the placenta and other developing organs and tissues, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., developing, neural, placental, brain, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 164 as residues: Pro-27 to Gly-34. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in placental tissue indicates the protein protein is useful in the detection, treatment, and/or prevention of vascular conditions, which include, but are not limited to, microvascular disease, vascular leak syndrome, aneurysm, stroke, atherosclerosis, arteriosclerosis, or embolism. For example, this gene product may represent a soluble factor produced by smooth muscle that regulates the innervation of organs or regulates the survival of neighboring neurons. Likewise, it is involved in controlling the digestive process, and such actions as peristalsis.

Similarly, it is involved in controlling the vasculature in areas where smooth muscle surrounds the endothelium of blood vessels. The expression within cellular sources marked by proliferating cells (e.g., infant cells and tissues) indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:45 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 972 of SEQ ID NO:45, b is an integer of 15 to 986, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:45, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 36

The translation product of this gene shares sequence homology with ion channel proteins which are thought to be important in many physiological processes including neural and muscular function (See, for example, Genebank Accession No. gi|1065507, and gb|AAC68885.1; all references available through these accession numbers are hereby incorporated herein; for example, FEBS Lett. 445, 231-236 (1999)). Specifically, this protein is homologous to the putative four repeat ion channel of Rattus norvegicus. Based upon the sequence similarity, The translation product of this gene is expected to share at least some biological activities with ion channel proteins. Such activities are known in the art, some of which are described elsewhere herein.

Preferred polypeptides comprise the following amino acid sequence: FYFITLIFFLAWLVKNVFIAVIIETFAEIRVQF (SEQ ID NO:347), SIFTVYEAASQEGWV (SEQ ID NO:348), and/or HEGTSIFTVYEAASQEGWVFL (SEQ ID NO:349). Also preferred are polynucleotides encoding these polypeptides.

This gene is expressed primarily in spinal cord.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the central and peripheral neurvous system, particularly neural degenerative conditions, and is useful in restoring cognitive function. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neural system, expression of this gene at significantly higher or lower levels is

routinely detected in certain tissues or cell types (e.g., neural, brain, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 165 as residues: Phe-8 to Ser-13, Ala-84 to Ser-90. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in spinal cord tissue, combined with the homology to ion channel proteins, indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:46 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1526 of SEQ ID NO:46, b is an integer of 15 to 1540, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:46, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 37

When tested against fibroblast cell lines, supernatants removed from cells containing this gene activated the early growth response gene 1 (EGR) pathway. Thus, it is likely that this gene activates fibroblast cells, and to a lesser extent, other cells and tissue cell-types, through the EGR signal transduction pathway. The early growth response gene is a separate signal transduction pathway from the Jaks-STAT, genes containing the EGR1 promoter are induced in various tissues and cell types upon activation, leading the cells to undergo differentiation and proliferation.

This gene is expressed primarily in uterus, colon cancer, synovium, fetal lung, and to a lesser extent in fetal and adult heart.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders of developing cells and tissues, particularly infertility and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing and reproductive systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, developing, gastrointestinal, synovium, skeletal, heart, lung, cardiovascular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative

to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 166 as residues: Lys-32 to His-38. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in developing and reproductive tissues, combined with the detected EGR1 biological activity, indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to certian types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:47 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 778 of SEQ ID NO:47, b is an integer of 15 to 792, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:47, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 38

Preferred polypeptides of the invention comprise the following amino acid sequence: CKTSFGLA (SEQ ID NO:350). Polynucleotides encoding these polypeptides are also provided. In an alternative embodiment, polypeptides of the invention comprise the following amino acid sequence: MITLSSAFSAKQKTHAHKNTHACM CATDMANPKLVLHFEVIVALLSLLQTILSLLLGQRTWLAHLYVLSTENXALHTVGTQKHLLPHDWCFGK HCVSCRHHIFHRFCSIFSSTLKRSQGFEG (SEQ ID NO:351). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in fetal bone, B and T cell lymphoma, and dendritic cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic, skeletal, and immune diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, skeletal, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, amniotic fluid, urine, synovial fluid and spinal fluid) or

another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 167 as residues: Ser-33 to His-42. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in T-cells and dendritic cells indicates polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:48 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or

more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1483 of SEQ ID NO:48, b is an integer of 15 to 1497, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:48, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 39

This gene is expressed primarily in prostate.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive diseases and/or disorders, partiuclarly prostate cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male reproductive system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, prostate, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, seminal fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 168 as residues: Pro-21 to Pro-26, Arg-31 to Asn-37. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in prostate tissue indicates that the protein products of this gene are useful for the diagnosis and intervention of prostate cancers, in addition to other tumors within the urogenital and reproductive system. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions,

in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:49 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1326 of SEQ ID NO:49, b is an integer of 15 to 1340, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:49, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 40

The translation product of this gene shares sequence homology with the human proliferating-cell nucleolar antigen as well as to a protein from Schizosaccharomyces pombe of unknown function (See Genebank Accession Nos. 189422 and gnl|PID|e349594, as well as Medline Article 90315275; all references available through these accessions are hereby incorporated herein by reference). This protein is the most cancer specific of the proliferation- associated nucleolar proteins identified thus far. In addition, it is of special interest because of its expression pattern in the early G1 phase, and, in studies prior to 1989, it has not been detected in benign tumors and most normal resting tissues.

In another embodiment, polypeptides of the invention comprise the following amino acid sequence:

SATEHGAVCCSCRRVGRRGEPPGSIKGLVYSSNFQNVKQLYALVCETQRYSAVLDAVIASAGLL
RAEKKLRPHLAKVLVYELLLGKGFRGGGGRWKALLGRHQARLKAELARLKVHRGVSRNEDLLEVGSRPG
P
ASQLPRFVRVNTLKTCSDDVVDYFKRQGFSYQGRASSLDDLRALKGKHFLLDPLMPELLVFPAQTDLHE
H
PLYRAGHLILQDRASCLPAMLLDPPPGSHVIDACAAPGNKTSHLAALLKNQGKIFAFDLDAKRLASMAT
L

LAXAGVSCCELAEEDFLAVSPXDPRYXEVHYXLLDPSCSGSGMPSRQLEXPGAGTPSPVRLHALAGFQQ
RALCHALTFPSLQRLVYSTCSLCQEENEDVVRDALQQNPGAFRLAPALPAWPHRGLSTFPGAEHCLRAS
PE TTLSSGFFVAVIERVEXPSSASQAKASAPERTPSPAPKRKKRQQRAAAGACTPPCT (SEQ ID
NO:356), CAAPGNKTSHLAA (SEQ ID NO:352), EHPLYRAGHLILQDRASCLPAMLL (SEQ
ID NO:353), LLDPSCSGSGMPSRQ (SEQ ID NO:354), YSTCSLCQEENEDVVRDALQQNP
(SEQ ID NO:355), and/or YEPHSTHSRERAMTSHARVSLGPSRDPLERPHLAKVLVYELLLGK
GFRGGGGRWKALLGRHQARLKAELARLKVHRGVSRNEDLLEVGSRPGPASQLPRFVRVNTLKTCSDDVV
DYFKRQGFSYQGRASSLDDLRALKGKHFLLDPLMPELLVFPAQTDLHEHPLYRAGHLILQDRASCLPAM
LLDPPPGSHVIDACAAPGNKTSHLAALLKNQGKIFAFDLDAKRLASMATLLAXAGVSCCELAEEDFLAV
SPXDPRYXEVHYXLLDPSCSGSGMPSRQLEEPGAGTPSPVRLHALAGFQQRALCHALTFPSLQRLVYST
CSLCQEENEDVVRDALQQNPGAFRLAPALPAWPHRGLSTFPGAEHCLRASPETTLSSGFFVAVIERVEV
PSSASQAKASAPERTPSPAPKRKKRQQXAAAGACTPPCT (SEQ ID NO:357).

Polynucleotides encoding these polypeptides are also provided. This gene maps to chromosome 7, and therefore, is used as a marker in linkage analysis for chromosome 7.

This gene is expressed primarily in T cells and rejected kidney and to a lesser extent in keratinocytes and various other normal and transformed, predominately haemopoietic cell types.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune diseases and/or disorders, particularly host-vs-graft disease, and transplant rejection. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., rejected transplant tissue, immune, heamtopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in T-cells and rejected kidney, indicates polynucleotides and polypeptides corresponding to this gene are useful for the

diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:50 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1525 of SEQ ID NO:50, b is an integer of 15 to 1539, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:50, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 41

The gene encoding the disclosed cDNA is believed to reside on chromosome 12. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 12.

This gene is expressed primarily in placenta, uterus, 12 week old, early stage, embryo and to a lesser extent in epithelium.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental and reproductive diseases and/or disorders, in addition to disorders of the integumentary system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developmental and epithelial tissues, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., developmental, reproductive, uterine, placental, integumentary, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, amniotic fluid, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in placental, uterine, and embyronic cells and tissues indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections

below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. The protein is useful for the detection, treatment, and/or prevention of various types of cancer, particularly of the integumentary system. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:51 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1409 of SEQ ID NO:51, b is an

integer of 15 to 1423, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:51, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 42

The translation product of this gene was shown to have homology to the human, bovine, mouse, and rat G protein gamma-3 subunit (See Genebank Accession Nos.W09413, pir|A36204|RGBOG3, gi|2582400 (AF022088), and gi|1353498) which are known to play a role in the regulation of signal transduction pathways. Moreover, the protein shares structural homology to a yeast mitochondrion membrane protein Q0225 (See Genbank Accession No. pir|S72689|S72689).

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

NREQKAKSQLLRSQLYSTLDLPYFFQCVGTRCTAVCVCVCVCVCVCX YLPIHWQVNLHLVYLAMLCFLPIPLLSILSPQTQASRLLDETVRRKHFLTYPFG ISSIITQALL (SEQ ID NO:360). Polynucleotides encoding these polypeptides are also provided.

In yet another embodiment, polypeptides of the invention comprise the following amino acid sequence: MGTHSVSGRFSKTSPPYCPPSSSLPGPISSIGFNKSLHECL FISEKELLPLPFPFPDLKSFISYLTSMLKPGPLIVSLKIWVSYPITRPRYLPPMLKSLNISFLYIQYIW AYIHLYTSFYIYIISVSFFLDKPFIYVISFPKPPHFLFASLSKTQEFHFHVPQHHFFLIFSPQVSSPIS CFARLLKSPLFTPVPTEISPFYNCAYYSADIPSPQLVWGPISHQTWLLLKLGLLPKRGFQVRGDRL (SEQ ID NO:358), and/or CFARLLKSPLFTPVPTEISPFYNCAYYSA (SEQ ID NO:359). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in infant brain, fetal tissue, frontal cortex, corpus collosum, and to a lesser extent in amygdala tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neural and CNS diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological

probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous and peripheral nervous systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 171 as residues: Thr-26 to Leu-33. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in various neural cells and tissues, combined with the similarity to G Protein Gamma-3 subunit indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as,

antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:52 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1350 of SEQ ID NO:52, b is an integer of 15 to 1364, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:52, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 43

The translation product of this gene shares homology with the human alpha-3 type IX collagen protein (See Genebank Accession No.gi|1196421). This protein likely represents a Type IIIb membrane protein. Although the preferred open reading frame of the present invention contains a signal peptide (as delineated in Table 1 and described elsewere herein), the protein appears to have several transmembrane domains. The transmembrane domains are located at about amino acid position 111 - 162, 137 - 162, 163 - 186, and 64 - 85 of the sequence referenced in Table 1 for this gene. Preferred are polypeptides comprising the following amino acid sequence: PGPEAQPWPGPDLPA VGSRGPGRLLAAVSAPRLGLGLAGADPVGPEACHLP (SEQ ID NO: 361), GRLRGPDEVGAPFHPGPATPGLADPLRPAEPXHWLPSLWGPT (SEQ ID NO: 362), PGPEAQPWPGPDLPAVGSR (SEQ ID NO: 363), and/or ATPGLADPLRPAEPXHWLP (SEQ ID NO: 364). Polynucleotides encoding these polypeptides are also provided.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

QWPEKDPVMAASSISSPWGKHVFKAILMVLVALILLHSALAQSRRDFAPP
GQQKREAPVDVLTQIGRSVRGTLDAWIGPETMHLVSESSSQVLWAISSAISVAFFALSGIAAQLLNALG
LAGDYLAQGLKLSPGQVQTFLLWGAGALVVYWLLSLLLGLVLALLGRILWGLKLVIFLAGFVALMRSVP

DPSTRALLLLALLILYALL SRXTGSRASGAQLEAKVRGLERQVEELRWRQRQXAKGARSVEEE (SEQ ID NO:365). Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome 11. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 11.

This gene is expressed primarily in melanocytes, and to a lesser extent in synovial sarcoma and larynx sarcoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, melanoma and other disorders of the integumentary system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the synovial and epithelial tissues, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., integumentary, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 172 as residues: Gln-15 to Phe-20, Pro-22 to Ala-30, Val-160 to Thr-165. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in melanocytes and sarcoma tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the study treatment and diagnosis of various cancers and their metastases, particularly of the integumentary system. Additionally, the homology to a conserved collagen protein would suggest that this protein may also be important in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias ie. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal

chondrodysplasia type Schmid. Moreover, polynucleotides and polypeptides corresponding to this gene are useful for the treatment, diagnosis, and/or prevention of various skin disorders. Representative uses are described in the "Biological Activity", "Hyperproliferative Disorders", "Infectious Disease", and "Regeneration" sections below, in Example 11, 19, and 20, and elsewhere herein. Briefly, the protein is useful in detecting, treating, and/or preventing congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e. keratoses, Bowen's disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's disease, mycosis fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e.wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, uticaria, eczema, photosensitivity, autoimmune disorders (i.e. lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma. In addition, such disorders may predispose increased susceptibility to viral and bacterial infections of the skin (i.e. cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, althletes foot, and ringworm). Moreover, the protein product of this gene may also be useful for the treatment or diagnosis of various connective tissue disorders (i.e., arthritis, trauma, tendonitis, chrondomalacia and inflammation, etc.), autoimmune disorders (i.e., rheumatoid arthritis, lupus, scleroderma, dermatomyositis, etc.), dwarfism, spinal deformation, joint abnormalities, amd chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:53 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2274 of SEQ ID NO:53, b is an integer of 15 to 2288, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:53, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 44

The translation product of this gene shares sequence homology with tumor progression inhibitor which is thought to be important in inhibition of tumor growth as well as its metastasis (See Genebank Accession No. W26667). Preferred are polypeptides comprising the following amino acid sequence:

EXPRXIXGXNAPQVPVRNSR

VDPRVRPRVRSLVFVLFCDEVRQWYVNGVNYFTDLWNVMDTLGLFYFIAGIVFRLHSSNKSSLYSGRVI FCLDYIIFTLRLIHIFTVSRNLGPKII (SEQ ID NO:366), NILLVNLLVAMF (SEQ ID NO:367), and/or QVWKFQRYFL (SEQ ID NO:368). Polynucleotides encoding these polypeptides are also provided.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

EXPRXIXGXNAPQVPVRNSRVDPRVRPRVRSLVFVLFCDEVRQWYVNGVNY

FTDLWNVMDTLGLFYFIAGIVFRLHSSNKSSLYSGRVIFCLDYIIFTLRLIHIFTVSRNLGPKIIMLQR

MLIDVXXFLFLFAVWMVAFGVAXQGILRQNEQRWRWIFRSVIYEPXLAMFGQVPSXVDGTTYDFAHCTF

TGNESKPLCVXLDEHNLPRFPEWITIPLVCIYMLSTNILLVNLLVAMFGYTVGTVQENNDQVWKFQRYF

LVQEYCSRLNIPFPFIVFAYFY MVVKKCFKCCCKEXNXESSVCCSKMXTMRLWHGRVS (SEQ ID NO:369). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in adult liver, prostate, gall bladder, and to a lesser extent, in Hodkin's lymphoma II.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, liver cancer and other hepatic diseases and/or disorders. Similarly,

polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the liver, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., hepatic, reproductive, metabolic, immune, hematpoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, bile, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in liver and gall bladder cells and tissues indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of liver disorders and cancers. Representative uses are described in the "Hyperproliferative Disorders", "Infectious Disease", and "Binding Activity" sections below, in Example 11, and 27, and elsewhere herein. Briefly, the protein can be used for the detection, treatment, and/or prevention of hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:54 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general

formula of a-b, where a is any integer between 1 to 1498 of SEQ ID NO:54, b is an integer of 15 to 1512, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:54, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 45

The polypeptide of the present invention is thought to have an intramitochondrial signal indicating that the protein could play a role in metabolic processes, including apoptosis. Based upon this fact, it is expected that the protein product of this gene will share at least some biological activities with other mitochondrial proteins having a similar signal. Such activities are known in the art, some of which are described elsewhere.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:
MEFQNMYIQLFGFSFFIVIIVRMLLLGLCVSARQPVMPRATLWGHLSPA
WVLVPWTPRACGQAAPGRGHVASDHKSGLPWPKHCSCLHPRASQPCLFSLNSNRTVFTAIQRVALGWTF
WVQANLVPRCT (SEQ ID NO:370). Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome 4. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 4.

This gene is expressed primarily in human prostate cancer, and to a lesser extent in soares melanocyte and human colon.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, prostate cancer, melanoma, and other diseases and/or disorders of the integumentary system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male reproductive system, expression of this gene

at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., prostate, reproductive, intregumentary, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, seminal fluid, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 174 as residues: Ser-36 to Gly-41, Pro-43 to Ser-49. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in tumors of prostate, colon, and integument origins indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. Representative uses are described elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:55 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1343 of SEQ ID NO:55, b is an integer of 15 to 1357, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:55, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 46

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

LLLCVTGVYSYGLMHPIPSSFMIKAVSSFLTAEEASVGNPEGAFMKVLQAR
KNXTSTELIVEPEEPSDSSGINLSGFGSEQLDTNDESDXISTLSYILPYFSAVNLDVXSXLLPFIKLPT
XGNSLAKIQTVGQNXQXVXRVLMGPRSIQKRHFKEVGRQSIRREQGAQASVENAAEEKRLGSPAPREXE
QPHTQQGPEKLAGNAXYTKPSFTQEHKAAVSVLXPFSKGAPSTSSPAKALPQVRDRWKDXTHXISILES
AKARVTNMKASKPISHSRKKYRFHKTRSRMTHRTPKVKKSPKFRKKSYLSRLMLANRPPFSAAXSLINS
PSQGAFSSLGDLSPQENPFLXVSAPSEHFIETTNIKDTTARNALEENVFMENTNMPEVTISENTNYNHP
PEADSXGTAFNLGPTVKQTET (SEQ ID NO:371). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in duodenum and cheek carcinoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, gastrointesinal disorders and carcinomas, in addition to disorders of the epithelium and mucosa. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., gastrointestinal, epithelial, mucosa, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in duodenal tissues and epithelia indicates that the protein product of this gene is useful for the diagnosis and intervention of tumors and other disorders within these tissues, in addition to other tumors. The expression within embryonic tissue and other cellular sources marked by proliferating cells indicates

this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:56 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1975 of SEQ ID NO:56, b is an integer of 15 to 1989, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:56, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 47

The translation product of this gene shares sequence homology with mouse magnesium dependent protein phosphatase (See Genebank Accession Nos. gnl|PID|d1004752 and emb|CAA06555.1| (AJ005458); all references available through these accessions are hereby incorporated herein by reference; for example, J. Neurosci. Res. 51 (3), 328-338 (1998)) which is thought to be important in normal

protein metabolism and possibly gene regulation. Based on the sequence similarity,

The translation product of this gene is expected to share at least some biological activities with phosphatase proteins. Such activities are known in the art, some of which are described elsewhere herein.

Preferred polypeptides comprise the following amino acid sequence: CFSNAPKVSDEAVKKDSELDKHLESRVEEIMEKSGEEGMPDLAHVMRILSAENIPNLPPGGGLAGXRNV IEAVYSRLNPHRESDGGAGDLEDPW (SEQ ID NO: 372), CFSNAPKVSDEAVKKDSELDKHLES RVEEIMEKSGEEGMPDLAHVMRILSAENIPN (SEQ ID NO: 373), RNVIEAVYSRLNPHRESDG GAGDLED (SEQ ID NO: 374), DSELDKHLESRVEEIM (SEQ ID NO: 375), KSGEEGMP DLAHVMRILSAENIPN (SEQ ID NO: 376), and/or CFSNAPKVS (SEQ ID NO: 377). Polynucleotides encoding these polypeptides are also provided.

A preferred polypeptide fragment of the invention comprises the following amino acid sequence: MSRKSLAFPIICSYLCFLTVATCSIACTTVFFANLRHTRYICIELSALET SGVISPQINNVPEVHGKYS (SEQ ID NO: 378). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in prostate and to a lesser extent in melanocytes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, proliferative conditions and cancers, in addition to reproductive, visual, and integumentary diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, visual, retinal, integumentary, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, aqueous humor, vitreous humor, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 176 as residues: Asp-6 to His-13, Asp-114 to Gly-131, Thr-166 to Gln-181, Val-210 to Thr-216, Pro-222 to Tyr-227. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in prostate tissue, combined with the homology to mouse magnesium dependent protein phosphatase indicates that polynucleotides and polypeptides corresponding to this gene are useful for the study and treatment of various cancers and reproductive disorders. This protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). This protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. The activity of this protein has been determined to be dependent upon the presence of magnesium ions. This protein is useful in the treatment, detection, and/or prevention of varoius visual disorders, particularly degenerative conditions, and retinitis pigmentosa. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:57 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2529 of SEQ ID NO:57, b is an integer of 15 to 2543, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:57, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 48

The translation product of this gene shares sequence homology with ribosomal protein L32 and L14, a mitochondrial protein from rat tissues thought to be important in translation (See Genebank Accession No.gi|868267). Preferred are polypeptides comprising the following amino acid sequence: IQKMTRVRVVDNSALG (SEQ ID NO: 379), PRCIHVYKKNGVGK (SEQ ID NO: 380), GDQILLAIKGQKKKA (SEQ ID NO: 381), and/or NPVGTRIKTPIPTSL (SEQ ID NO: 382). Polynucleotides encoding these polypeptides are also provided.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

VLIPSFSSSFLCSRGGPLPXDLSWDPMAFFTGLWGPFTCVSRVLSHHCF
STTGSLSAIQKMTRVRVVDNSALGNSPYHRAPRCIHVYKKNGVGKVGDQILLAIKGQKKKALIVGHCMP
GPRMTPRFDSNNVVLIEDNGNPVGTRIKTPIPTSLRKREGEYSKVLAIAQNFV (SEQ ID NO: 383). Polynucleotides encoding these polypeptides are also provided. This gene maps to chromosome 6, and therefore, is used as a marker in linkage analysis for chromosome 6.

This gene is expressed primarily in uterus, fetal liver/spleen, human endometrial stromal cells-treated with estradiol and amniotic cells - Primary Culture, and to a lesser extent in, human fetal kidney.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, endometriosis and reproductive disorders, particularly of the female reproductive system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the female reproductive system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., uterine, endometrium, reproductive, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 177 as residues: Pro-92 to Ser-102, Leu-127 to Tyr-134. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in endometrium and uterine tissues, combined with the homology to a ribosomal protein indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of tumors within said tissue, in addition to other tumors where expression has been indicated. This protein may play a role in cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this

gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Antagonists, including antobodies directed against this invention, is useful in inhibiting cellular proliferation and thus is useful in inhibiting cancers, in addition to other proliferative diseases and/or disorders. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:58 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 763 of SEQ ID NO:58, b is an integer of 15 to 777, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:58, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 49

This gene is expressed primarily in liver, hepatoma and to a lesser extent in epithelial-TNFa and INF induced.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, liver diseases and/or disorders, particularly cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hepatic system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., hepatic, liver, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 178 as residues: Glu-28 to Gly-45, Ser-63 to Gly-69, Gln-96 to Trp-104, Gly-112 to Pro-117, Arg-121 to Pro-128. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in liver and hepatoma tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). Representative uses are described in the "Hyperproliferative Disorders", "Infectious Disease", and "Binding Activity" sections below, in Example 11, and 27, and elsewhere herein. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:59 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 865 of SEQ ID NO:59, b is an integer of 15 to 879, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:59, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 50

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

ARVVQPAARAGMWAGGRSSCQAEVLRATRGGAARGNAAPGRALEMVPGAAG
WCCLVLWLPACVAAHGFRIHDYLYFQVLSPGDIRYIFTATPAKDFGGIFHTRYEQIHLVPAEPPEACGE
LSNGFFIQDQIALVERGGCSFLSKTRVVQEHGGRAVIISDNALTMTASTWR (SEQ ID NO: 384).

Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome 2. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 2.

This gene is expressed primarily in breast lymph node, ovary, osteoclast cells, and to a lesser extent in human jurkat membrane-bound polysomes and human placenta.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, breast cancer and immune diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, endocrine, skeletal, bone, placental,

and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, amniotic fluid, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in human breast and placental tissue indicates that the protein product of this gene is useful for diagnosis and intervention of tumors within these tissues, in addition to other tumors and tissues where expression has been indicated. Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:60 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1147 of SEQ ID NO:60, b is an integer of 15 to 1161, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:60, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 51

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the

following amino acid sequence:

IATAALFFFFYCQVAGFIGKGQSLRSWVPQRLLGLEPQLQPMQQSRLLLP
FLFFLLEGCAPSSLGPGAAPGSGHSLGPPGSPGAPGPQPAVGPSSPCQPGPSPSSPAAAAASSQSSVAS
WPCTLRCAAPSPDASALRPAASPAATPAWSPGSGTIRVLRPPAPAAAPATAITNRGPPRRRRRNARTA

(SEQ ID NO: 385). Polynucleotides encoding these polypeptides are also provided.

In yet another embodiment, polypeptides of the invention comprise the following amino acid sequence: ERPPPRRTGTPVARPRGPPDPAVAAGTALRAKQFARYGAASG
VVPGSLWPSPEQLRELEAEEREWYPSLATMQESLRVKQLAEEQKRREREQHIAECMAKMPQMIVNWQQQ
QRENWEKAQADKERRARLQAEAQELLGYQVDPRSARFQELLQDLEKKERNPQGGKTETEEGGATAALAA
AVAQDPAASGAPSS (SEQ ID NO: 386). Polynucleotides encoding these polypeptides are also provided. The polypeptide sequence of the latter embodiment was found to have homology to the human HPK/GCK-like kinase HGK (See Genbank Accession No. gb|AAD16137.1| (AF096300); all references available through this accession are hereby incorporated herein by reference; for example, J. Biol. Chem. 274 (4), 2118-2125 (1999)) which is thought to play a role in modulating gene expression, particularly for genes involved in the c-jun pathway. Based on the sequence similarity, The translation product of this gene is expected to share at least some biological activities with signalling and kinase proteins. Such activities are known in the art, some of which are described elsewhere herein.

The gene encoding the disclosed cDNA is believed to reside on chromosome 19. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 19.

This gene is expressed primarily in HL-60, PMA 4H and to a lesser extent in Soares breast 2NbHBst, Human Pituitary, subt IX, and Human Fetal Kidney.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune, hematopoietic, developmental, and proliferative diseases and/or disorders, particularly promyelocytic leukemia. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain

tissues or cell types (e.g., immune, hematopoietic, reproductive, developmental, proliferative, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 180 as residues: Ser-54 to Ser-63, Asn-132 to Thr-145. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in HL-60 cells indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of

various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:61 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 673 of SEQ ID NO:61, b is an integer of 15 to 687, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:61, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 52

The translation product of this gene shares sequence homology with the human hypothetical L1 protein (third intron of gene TS) (See Genebank Accession No. pir|JU0033|JU0033), which is thought to be important for the regulation of RNA-dependent DNA polymerases.

Preferred polypeptides comprise the following amino acid sequence: YQSLAETQQKKENFRPISLKNTDAKILNKILANQIQQHIKKLIHNDRVGFIPEMQGWFNICKSINIVHH INRTKDKNHMIISIDAEKAFDKIRQSFMLKTLNKLGIHGMYLGR (SEQ ID NO: 387), KKENFR PISLKNTDAKILNKILANQIQQHIKKLIHNDRVGFIPEMQGWFNICKSINIVHHINRTKDKNHMIISID AEKAFDKIRQSFMLKTLNKLGIHGMY (SEQ ID NO: 388), DAKILNKILAN (SEQ ID NO: 389), IQQHIKKLIH (SEQ ID NO: 390), KDKNHMIISIDAEKAFDKI (SEQ ID NO: 391), MLKTLNKLGI (SEQ ID NO: 392), and/or KKENFRPISL (SEQ ID NO: 393). Polynucleotides encoding these polypeptides are also provided.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: WTMFIDLHMLNQPCISGMKPTRSL

WISFLMCCWIWFANILLRIFASVFFRDIGLKFSFFCCVSARLWYQDDAGLINEL GRIPSFY (SEQ ID NO: 394). Polynucleotides encoding these polypeptides are also provided. The presence of the amino acid sequences upstream of the predicted signal sequence of the latter embodiment may alter the characteristics of the protein of the present invention such that either the full protein, or fragments thereof, are bound to the membrane in a form analagous to a Type II membrane protein. This form of the protein is thought to have a cytoplasmic tail covering about the first 21 amino acids. Based on the structural similarity, the translation product of this latter embodiment is expected to share at least some biological activities with type II membrane proteins. Such activities are known in the art, some of which are described elsewhere herein.

This gene is expressed primarily in ulcerative colitis.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, gastrointestinal diseases and/or disroders, particularly ulcerative colitis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., gastrointestinal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, chyme, bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in ulcerative colon tissue combined with its homology to an RNA-dependent DNA polymerase regulatory protein may suggest that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of tumors and other proliferative conditions within the indicated tissues, and to a lesser extent in other tissues and cell types. Moreover, the expression within cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis,

treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:62 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 504 of SEQ ID NO:62, b is an integer of 15 to 518, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:62, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 53

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

ERPEEGTEPSPSPVAEQASVSMTPVFRAWGLWVYVLPTGFPGPCCMMLLEL FPKESVPQAYQGILLYLHFGF (SEQ ID NO: 395). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in ovary, testis, Hodkin's lymphoma, resting T-Cell; re-excision and to a lesser extent in soares multiple sclerosis, human corpus colosum, and fetal kidney.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive, immune, and hematopoietic diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, ovarian, testicular, breast, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, seminal fluid, breast milk, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in testicular tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that is expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product is expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. Moreover,the protein product of this gene has also been shown to be expressed in ovary and breast tissue which, in combination with the detected expression in testis, indicates that this protein represents a secreted factor

that plays an important role in proper reproduction (e.g., hormone, signalling factor, etc.). Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:63 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 897 of SEQ ID NO:63, b is an integer of 15 to 911, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:63, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 54

When tested against U937 cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates myeloid cells, and to a lesser extent, other cells and tissue cell-types, through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: RGE VPHQPHPTRRTVVSGQAPWXPGPXALGQXVETAAGMGMPLVTVTAATFPTL

SCPPRAWPEVEAPEAPALP
VVPELPEVPMEMPLVLPPELELLSLEAVHRYQXGGTLMGWTRAEASANGS (SEQ ID NO: 396). Polynucleotides encoding these polypeptides are also provided. In yet another embodiment,

Preferred polypeptides of the invention comprise the following amino acid sequence: MVLDPYRAVALELQANREPDFSSLVSPLSPRRMAARVFYLLLGECMHVCVCMWGRDTET RGPYRDSPDLPSPRLLTSALSATDSSRETRKAIWSPPDPAGAQIPLRLESIYKAARKPATSSKPRRASL KKKKK (SEQ ID NO: 397). Polynucleotides encoding these polypeptides are also provided. Polypeptides of the latter embodiment share homology to the human hHR21spB (See Genbank Accession No.gi|4101480|gb|AAD01193.1| (AF006264); all references available through this accession are hereby incorporated by reference herein) which is thought to play a role in DNA repair. Based on the sequence similarity, The translation product of this gene is expected to share at least some biological activities with DNA repair proteins. Such activities are known in the art, some of which are described elsewhere herein.

The gene encoding the disclosed cDNA is believed to reside on chromosome 22. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 22.

This gene is expressed primarily in resting T-Cells, testis, uterine cancer, bone marrow, and to a lesser extent in cerebellum.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune, reproductive, and neural diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, neural, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, seminal fluid, amniotic fluid, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene

expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in bone marrow and resting T-cells, combined with the detected GAS biological activity, indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as,

antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:64 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 949 of SEQ ID NO:64, b is an integer of 15 to 963, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:64, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 55

The translation product of this gene was shown to have homology to the human platelet membrane glycoprotein V, which is a part of the Ib-V-IX system of surface glycoproteins (GPs Ib alpha, Ib beta, V, IX) that constitute the receptor for von Willebrand factor (vWf) and mediate the adhesion of platelets to injured vascular surfaces in the arterial circulation, a critical initiating event in hemostasis (See Genebank Accession No.gi|388760). Moreover, the protein product of this gene was also shown to have homology to human toll and toll-like receptors (See Genbank Accession Nos. W86352, and gb|AF051151|AF051151; all references available through this accession are hereby incorporated herein by reference; for example, Blood 91 (11), 4020-4027 (1998)). Based on the sequence similarity, The translation product of this gene is expected to share at least some biological activities with toll-receptor proteins. Such activities are known in the art, some of which are described elsewhere herein. Preferred are polypeptides comprising the following amino acid sequence: AFRNLPNLRIL (SEQ ID NO: 398), and/or AFQGLFHLFELRL (SEQ ID No: 399). Polynucleotides encoding these polypeptides are also provided.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by

the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

NKXILEVPSARTTRIMGDHLDLLLGVVLMAGPVFGIPSCSFDGRIAFYR
FCNLTQVPQVLNTTERLLLSFNYIRTVTASSFPFLEQLQLLELGSQYTPLTIDKEAFRNLPNLRILDLG
SSKIYFLHPDAFQGLFHLFELRLYFCGLSDAVLKDGYFRNLKALTRLDLSKNQIRSLYLHPSFGKLNSL
KSIDFSSNQIFLVCEHELE (SEQ ID NO: 400). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in pancreatic tumors.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, pancreatic cancer; impaired pancreatic function; altered carbohydrate metabolism; and immune and hematopoietic diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the pancreas or endocrine system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., pancreatic, gastrointestinal, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, bile, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in pancreatic tumors indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of disorders of the pancreas. Expression of this gene product in pancreas tumors indicates a potential involvement in pancreatic cancer, and indicates that the gene product may play more general roles in cellular proliferation and/or apoptosis as well. Alternately, expression in the pancreas may suggest a general involvement in pancreatic function, and implicate the utility of this gene product in a variety of pancreatic disorders. Alternately, as this protein is a secreted protein, it may simply be produced by the pancreas to have effects at other sites within the body or endocrine

system. In addition, the homology to a conserved receptor for for von Willebrand factor indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoetic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. The product of this gene may also show utility in the treatment of vascular diseases such as athlerosclerosis and stroke. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:65 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 987 of SEQ ID NO:65, b is an integer of 15 to 1001, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:65, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 56

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by

the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

AHAALQLSLRTCGPCSSPYPHAGLAALLTHMWALQLSLPTCGLAALLTHMRPCSSPYPHAGLAALLTHM
GPCRSPYPHGGLAAVLTHMRALQLSLPTWGLAALLTHMRPCSSPYPHAGLACCWLWSLSSHRSLQVQAT
HRLVVRTIKDRVMLKVLPQTRRRGPFLSSCRNDVMRNCVPRHAVLVTTCVFVSFPTHCKVGITGPITQV
KQKPGNHSSPCPVIQLVAKAEFELMLPSVPKPVYLTLVLSCWCLCDVPCLSVSL (SEQ ID NO: 401). Polynucleotides encoding these polypeptides are also provided. It has been determined that the protein product of this gene has a conserved G-protein receptor motif beginning at amino acid position 89 and ending at amino acid position 105 of the amino acid sequence referenced in Table 1 for this gene.

Preferred polypeptides of the invention comprise the following amino acid sequence: LACCWLWSLSSHRSLQV (SEQ ID NO: 402). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in tonsils and anergic T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune system disorders; immune dysfunction; impaired immune surveillance. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 185 as residues: Pro-22 to Pro-28, Pro-41 to His-48, Pro-79 to His-86, Pro-126 to Phe-134, Ser-137 to Met-143, Gln-176 to Ser-186. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in T-cells and tonsils, combined with the identification of a G-protein receptor motif within the open reading frame, indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:66 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1544 of SEQ ID NO:66, b is an integer of 15 to 1558, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:66, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 57

This gene is expressed primarily in healing groin wound (6.5 hours post incision), and to a lesser extent in testis.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, wounded tissues; disorders involving tissue repair; male reproductive disorders; mucositis; tissue degeneration. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, testis, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, seminal fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 186 as residues: Ser-59 to Gly-68. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in healing groin wound and testis indicates that polynucleotides and polypeptides corresponding to this gene are useful for therapeutic use as an agent to facilitate wound healing and tissue regeneration. Expression of this product during wound healing indicates that it may play a beneficial role during the

process. Alternately, expression during wound healing may also suggest that it plays a negative role during the process, e.g. fibrosis and scarring, and that therapeutics designed to counter the effects of this protein is even more beneficial. In addition, expression of this protein within the groin and testis indicates that it may play a role in reproductive system function - particularly male reproductive function - and that this protein may even have potential uses as a male contraceptive. Alternately, The tissue distribution in testicular tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that is expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product is expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:67 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1308 of SEQ ID NO:67, b is an

integer of 15 to 1322, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:67, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 58

A preferred polypeptide fragment of the invention comprises the following amino acid sequence: MGEASPPAPARRHLLVLLLLLSTLVIPSAAAPIHDADAQESSLGLTGLQS LLQGFSRLFLKVTCFGA (SEQ ID NO: 403). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in testis, and to a lesser extent in brain and fetal heart.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative disorders; psychological disorders; learning disabilities; altered heart function; altered male reproductive function. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain and nervous system, cardiovascular system, or reproductive system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, testis, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, seminal fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 187 as residues: Pro-82 to His-93. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in testicular tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment

of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that is expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product is expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. Alternatively, The tissue distribution in brain indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of brain and nervous system disorders. Expression of this gene product in a variety of brain regions indicates a role in brain and nervous system function. This indicates that the protein product is useful in the treatment of neurodegenerative disorders; learning disabilities; psychoses; and behaviours, including feeding; sleeping; perception; balance; etc. Therefore, this gene product is useful in the treatment of a variety of heart conditions, including myocardial infarction; congestive heart failure; arrhythmias; coronary occlusion; and a variety of other disorders of the heart. The secreted protein can also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, and as nutritional supplements. It may also have a very wide range of biological activities. Representative uses are described in the "Chemotaxis" and "Binding Activity" sections below, in Examples 11, 12, 13, 14, 15, 16, 18, 19, and 20, and elsewhere herein. Briefly, the protein may possess the following activities: cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of hematopoiesis (e.g. for treating anemia or as adjunct to chemotherapy); stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors); hemostatic or thrombolytic activity (e.g. for treating hemophilia, cardiac infarction

etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's disease); as antimicrobials; for treating psoriasis or other hyperproliferative diseases; for regulation of metabolism, and behavior. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:68 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 851 of SEQ ID NO:68, b is an integer of 15 to 865, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:68, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 59

The translation product of this gene shares sequence homology with alpha 1,3 galactosyltransferase which is thought to be important in the regulation of protein glycosylation and sugar transfer (See Genebank Accession No. bs|150271; all references available through this accession are hereby incorporated by reference herein).

Preferred polypeptides comprise the following amino acid sequence: MLVVSTVIIVFWEFINSTEGSFLWIYHSKNPEVDDSSAQKGWWFLSWFNNGIHNYQQGEEDIDKEKGRE ETKGRKMTQQSFGYGTGLIQT (SEQ ID NO: 404), and/or FPGRTHASGNVKGKVILS (SEQ ID NO: 405). Polynucleotides encoding these polypeptides are also provided.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by

the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

ADQEKIRNVKGKVILSMLVVSTVIIVFWEFINSTEGSFLWIYHSKNPEV

DDSSAQKGWWFLSWFNNGIHNYQQGEEDIDKEKGREETKGRKMTQQSFGYGTGLIQT (SEQ ID NO: 406). Polynucleotides encoding these polypeptides are also provided. The presence of the upstream amino acids of the latter embodiment may significantly alter the secreted characteristics of the present invention. Namely, either the full-length protein, or fragments thereof, iscome membrane bound in a mechanism analagous to type II membrane proteins. Based on the such characteristics, the translation product of this latter embodiment is expected to share at least some biological activities with type II membrane proteins. Such activities are known in the art, some of which are described elsewhere herein. fragments.

The gene encoding the disclosed cDNA is believed to reside on chromosome 9. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 9.

This gene is expressed primarily in primary dendritic cells, neutrophils, and T cells and to a lesser extent in liver hepatoma and infant brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune dysfunction, hematopoietic disorders; inflammation; neurodegenerative disorders; liver hepatoma; T cell lymphoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, liver, or CNS, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 188 as residues: His-27 to Gly-41, Gln-56 to Tyr-83. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in dendritic cells, combined with the homology to galactosyltransferases indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of a variety of disorders, particularly of the immune and nervous systems since normal function of such tissues depends upon proper glycoprotein recognition and galactosyltransferase function. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Expression of this gene product in dendritic cells indicates a role in the regulation of the immune system and responses to infectious agents. This may involve roles in antigen presentation, antigen processing, stimulation and activation of B and T cells, or stimulation/activation of dendritic cells themselves. This is evidenced by effects on cytokine production. Expression of this gene product in other hematopoietic cells such as T cells and neutrophils also indicates roles in the functions of those cells as well, and involvement in the proliferation, survival, and/or differentiation of hematopoietic cells in general. In addition, the expression also indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoetic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses may include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. Expression of this gene product within infant brain also indicates a role in neuron survival, synapse formation, neurotransmission, perception, etc. The protein is useful in the treatment and/or prevention of degenerative myelinating diseases and/or disorders, particularly multiple sclerosis, in addition to other disorders which occur secondary to aberrant fatty-acid metabolism. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or

receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:69 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1136 of SEQ ID NO:69, b is an integer of 15 to 1150, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:69, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 60

This gene is expressed primarily in small intestine and leukocytes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic disorders; inflammation; allergy; impaired immunity; autoimmunity, and gastrointestinal disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., gastrointestinal, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in leukocytes indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of a variety of hematopoietic disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Expression of this gene product in small intestines and leukocytes indicates that it is expressed by various hematopoietic cells, for example, in the peyer's patches of intestine as well as within the circulation itself. Thus, it may play a role in the proliferation; survival; differentiation; or activation of various hematopoietic cell lineages. This may affect the cells' ability to recognize antigen; mount an immune response; participate in inflammatory processes; and effectively patrol the body for infectious or foreign agents. Alternately, expression of this gene product in small intestine may reflect a role in digestion and food processing. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:70 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1384 of SEQ ID NO:70, b is an integer of 15 to 1398, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:70, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 61

The translation product of this gene shares sequence homology with the Drosophila strabismus gene product which is thought to regulate tissue polarity and cell fate decisions (See Genebank Accession No.gi|2854044 (AF044208); all

references available through this reference are hereby incorporated herein by reference). When tested against U937 cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates myeloid cells, and to a lesser extent, other cells and tissue cell types, through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

Preferred polypeptides of the invention comprise the following amino acid sequence: MQSPLVECPPPSIHYWPSVPAGAQGACSPMFHAAGWSRSQPNGEIPASSXGHLSIQRAAL VVLENYYKDFTIYNPNLLTASKFRAAKHMAGLKVYNVDGPSNNATGQSRAMIAAAARRRDSSHNELYYE EAEHERRVKKRKARLVVAVEEAFIHIQRLQAEEQQKAPGEVMDPREAAQAIFPSMARALQKYLRITRQQ NYHSMESILQAPGLLHHQRHDPQGLPRTVPQCGPHPAI (SEQ ID NO: 407), LSIQRAALVV LENYYKDFTIYNP (SEQ ID NO: 408), DSSHNELYYEEAEHE (SEQ ID NO: 409), and/or FPSMARALQKYLRITRQQ (SEQ ID NO: 410). Polynucleotides encoding these polypeptides are also provided.

A preferred polypeptide fragment of the invention comprises the following amino acid sequence: MAFKLLILLIGTWALFFRKRRADMPRVFVFRALLLVLIFLFCGFPIGFFT GSAFWTLGNRNYQGIVQYAVSPCGMPSSFHPLLAIRPCWSSGSLQPNVPRCRLVPLPTEWGNPRFQXGT PEYPASSIGGPRKLLQRFHHL (SEQ ID NO: 411). Polynucleotides encoding these polypeptides are also provided.

The translation product of this gene was determined to have a transmembrane domain located at amino acid position 249 - 266 of the amino sequence referenced in Table 1 for this gene. Likewise, this protein is thought to be a Type II membrane protein.

This gene is expressed primarily in human osteoclast stromal cells, fetal liver and spleen, and in endometrial tumors and to a lesser extent in hematopoietic cells, including T-cells and CD34 positive cells isolated from cord blood, as well as the thymus, fetal heart, 8 week old whole embryos, and tumors of pancreatic and testicular origin.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune system disorders, including AIDS and other hematopoietic diseases and/or disorders, in addition to tumors of osteoclast, endometrial, pancreatic, or testicular origin. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system as well as biological processes involved in cellular proliferation and/or differentiation, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, haematopoeitic, skeletal, cancerous, and/or other tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid, lymph, breast milk, and/or seminal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 190 as residues: Pro-17 to Gln-24, Asp-86 to Ser-96, Arg-106 to Asn-112, Ala-119 to Ala-130, Ala-148 to Pro-155, Gln-223 to Leu-230. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in immune cells and tissues, combined with the detected GAS biological activity, indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the

natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Alternatively, the tissue expression in liver tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various would-healing models and/or tissue traumas. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:71 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general

formula of a-b, where a is any integer between 1 to 1543 of SEQ ID NO:71, b is an integer of 15 to 1557, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:71, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 62

A preferred polypeptide fragment of the invention comprises the following amino acid sequence: MGLPVSWAPPALWVLGCCALLLSLWALCTACRSPRTL (SEQ ID NO: 412). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in human thymus, human synovial sarcoma,and to a lesser extent in breast cancer cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune diseases and/or disorders, particularly autoimmune disorders such as arthritis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 191 as residues: Pro-40 to Arg-50, Ser-72 to Arg-77, His-82 to Leu-91, Gln-171 to Glu-189, Val-203 to Gly-222, Pro-263 to Thr-269, Ser-282 to Trp-287. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in thymus indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19,

20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in cancerous and/or proliferative cells and tissues. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:72 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or

more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1149 of SEQ ID NO:72, b is an integer of 15 to 1163, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:72, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 63

The translation product of this gene shares sequence homology with human, porcine, and mouse zona pellucida binding protein sp 38 which is known to be important in sperm binding to the zona pellucida of an egg cell. Monoclonal antibodies directed against this protein have resulted in inhibition of the sperm/egg binding reaction. As such The translation product of this gene may show commercial utility as a contraceptive. (See Genebank Accession No. gnl|PID|d1005021; all references available through this accession are hereby incorporated by reference herein).

Preferred polypeptides of the invention comprise the following amino acid sequence: IYGKTGQPDKIYVELHQNSP (SEQ ID NO: 413), FLEPLSGLYTCTLSYK (SEQ ID NO: 414), LQVVRLDSCRPGFGKN (SEQ ID NO: 415), and/or CVSVLTYGAKSC (SEQ ID NO: 416). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in a human testes library. It has not been found in other libraries screened at HGS.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, infertility, and/or other reproductive diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male and female reproductive systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., testes, and cancerous and wounded tissues) or bodily fluids (e.g. seminal fluid, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression

level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 192 as residues: Lys-35 to Asp-40, Pro-75 to Asn-84, Lys-114 to Arg-129, Arg-138 to Ser-143, Ser-154 to Asn-160, Val-224 to Asn-231, Arg-238 to Asp-243, Asp-276 to Asn-291, Lys-324 to Asp-338. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in testes combined with the homology to the human, porcine, and mouse zona pellucida protein Sp 38 indicates that polynucleotides and polypeptides corresponding to this gene are useful for the production of a contraceptive vaccine. Alternatively, the protein may show utility in the diagnosis, treatment, and/or prevention of a variety of reproductive disorders within both the male and female reproductive systems. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that is expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product is expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:73 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or

more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1472 of SEQ ID NO:73, b is an integer of 15 to 1486, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:73, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 64

When tested against U937 cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates myeloid, and to a lesser extent, other cells and tissue cell types, through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

This gene is expressed primarily an apoptotic T-cell library, and to a lesser extent, in whole embryo.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune, hematopoietic, and developmental diseases and/or disorders, particularly disorders related to aberrant cell death regulation. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, developmental, reproductive, apoptotic cells, and cancerous and healing tissue or cells) or bodily fluids (e.g., serum, lymph, amniotic fluid, plasma, urine, synovial fluid and spinal fluid, and/or lymph) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 193 as residues: Met-1 to Ala-6, Gly-51 to Gly-71. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in apoptotic T-cells indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the

protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:74 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1539 of SEQ ID NO:74, b is an integer of 15 to 1553, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:74, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 65

The translation product of this gene shares sequence homology with a 50 kDa glycoprotein of the human erythrocyte membrane associated blood-group antigen which is thought to have a transport or channel function in the erythrocyte membrane (See GenBank No. gb|X64594|HSEPMG50; all references available through this accession are hereby incorporated herein by reference). When tested against Jurkat cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates T-cells, and to a lesser extent, other cells and tissue cell types, through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. The translation product of this gene has been determined to contain two transmembrane domains located at amino acid positions 95 - 124, and 1 - 27 of the amino acid sequence referenced in Table 1 for this gene. Therefore, this protein may share structural characteristics to Type IIIa membrane protein. Based on the sequence similarity to the human erythrocyte membrane

associated blood-group antigen, and the structural similarity to type IIIa membrane proteins, The translation product of this gene is expected to share at least some biological activities with such proteins. Such activities are known in the art, some of which are described elsewhere herein.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

PAKGEGCRRLHDHPHIWRLLWAHSDPDPLPTQPRAEQGETEFCVPVGPLCH
DWHPLPVDVLAQLQLSHILPWGQPAPSRHQHLLLLGSLRAYLGGNIQCPAKKGKLDMVHIQNATLAGGV
AVGTAAEMMLMPYGALIIGFVCGIISTLGFVYLTPFLESRLHIQDTCGINNLHGIPGIIGGIVGAVTAA
SASLEVYGKEGLVHSFDFQGFNGDWTARTQGKFQIYGLLVTLAMALMGGIIVGLILRLPFWGQPSDENC
FEDAVYWEMPEGNSTVYIPEDPTFKPSGPSVPSVPMVSPLPMASSVPLVP (SEQ ID NO: 417).

Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome 18. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 18.

This gene is expressed primarily in in tonsils and to a lesser extent in the larynx, kidney medulla, epithelial cells, keratinocytes, and cells involved in hematopoiesis, especially neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic diseases and/or disorders, in addition to, the proliferation and/or differentiation of integumentary cells. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., haematopoetic, integumentary, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid, lymph) or another tissue or cell sample taken from an individual having such a

disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 194 as residues: Gly-85 to Lys-94, Gln-125 to Cys-131, Glu-151 to Gly-159. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in tonsils, combined with the homology to a 50 kDa glycoprotein of the human erythrocyte membrane protein indicates polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:75 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general

formula of a-b, where a is any integer between 1 to 1636 of SEQ ID NO:75, b is an integer of 15 to 1650, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:75, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 66

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

PRVRTRAPVVPPAGHRALSPAGVLLAVPAMLSLDFLDDVRRMNKRQVSLS VLFFSWLFLSLRGCCCGARRTPGFWCEGLSWSDTRVIRFLWRLWPEAALSASLFLTPN (SEQ ID NO: 418). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in hematopoietic tissues, especially helper T-cells and anergic T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, tuberculosis, AIDS, and other immune diseases and/or disorders, particularly infections and/or malignancies. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., haematopoeitic, immune, and cancerous, and/or wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid, and/or lymph) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 195 as residues: Asp-9 to Gln-17. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in immune cells and tissues indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:76 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2136 of SEQ ID NO:76, b is an integer of 15 to 2150, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:76, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 67

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 15 - 34 of the amino acid sequence referenced in Table 1 for this gene. Moreover, a cytoplasmic tail encompassing amino acids 1 - 14 of this protein has also been determined. Based upon these characeristics, it is believed that the protein product of this gene shares structural features to type II membrane proteins.

This gene is expressed primarily in the fetal liver/spleen, human brain, and retina.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune, neurologic, and visual diseases and/or disorders, particularly retinoblastoma as well as other diseases or disorders involving the retina and/or brain. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neurologic system and in eye development, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, visual, retinal, neural, cancerous, and/or wounded tissues) or bodily fluids (e.g., serum, plasma, aqueous humor, vitreous humor, urine, amniotic fluid, synovial fluid and spinal fluid, vitreous and aqueous humors) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 196 as residues: Glu-48 to Thr-54. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in fetal liver/spleen indicates polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Alternatively, representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Alternatively, expression of this gene with in the retina may suggest gene is useful for the diagnosis, treatment, and/or prevention of a variety of eye disorders and/or conditions. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or

immunotherapy targets for the above listed tissues. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:77 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1578 of SEQ ID NO:77, b is an integer of 15 to 1592, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:77, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 68

The translation product of this gene shares sequence homology with the glutamate-binding subunit of an N-methyl-D-asparate receptor complex. The amino acids L-glutamic and L-aspartic acids form the most widespread excitatory transmitter network in mammalian brain. The excitation produced by L-glutamic acid is important in the early development of the nervous system, synaptic plasticity and memory formation, seizures and neuronal degeneration. The receptors activated by L-glutamic acid are a target for therapeutic intervention in neurodegenerative diseases, brain ischaemia and epilepsy. As such, the protein product of this gene may also play a role in the regulation of the nitrous oxide synthase gene which is known to be a vital link in various signal transduction pathways within the brain as well as other tissues (See GenBank No. bbs|61979 and Medline Article No.92049755). Moreover, The translation product of this gene was also shown to have homology to a neural membrane protein 35 (See Genbank Accession No. gb|AAC32463.1| (AF044201); all references available through this accession are hereby incorporated herein by

reference; for example, Mol. Cell. Neurosci. 11 (5), 260-273 (1998)). The polypeptide of this gene has been determined to have two transmembrane domains at about amino acid position 42 - 73, and 75 - 94 of the amino acid sequence referenced in Table 1 for this gene. Based upon these characeristics, it is believed that the protein product of this gene shares structural features to IIIa membrane proteins. When tested against U937 and Jurkat cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates myeloid and T-cells, and to a lesser extent, other cells and tissue cell types, through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

Preferred polypeptides of the invention comprise the following amino acid sequence: HASAWNLILLTVFTLS (SEQ ID NO: 419), VYAALGAGVFTLFLALDTQLLMGN (SEQ ID NO: 420), EEYIFGALNIYLDIIYIF (SEQ ID NO: 421), and/or WNLILLTVFTLSMAYLTGMLSSYYNT (SEQ ID NO: 422). Polynucleotides encoding these polypeptides are also provided.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

MAYLTGMLSSYYNTTSVLLCLGITALVCLSVTVFSFQTKFDFTSCQGVLF VLLMTLFFSGLILAILLPFQYVPWLHAVYAALGAGVFTLFLALDTQLLMGNRRHSLSPEEYIFGALNIY LDIIYIFTFFLQLFGTNRE (SEQ ID NO: 242). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in the brain and to a lesser extent in dendritic cells and in the kidney cortex.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, schizophrenia, epilepsy, brain ischaemia, and neurodegenerative diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g.neural, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 197 as residues: Ala-12 to Glu-27, Pro-35 to Ser-43, Pro-70 to Gly-79, Ser-92 to Val-98, Pro-166 to Leu-175, Ser-234 to Thr-246. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution combined with the homology to a known N-methyl-D-asparate receptor indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. This protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment,

and/or prevention of developmental diseases and disorders. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:78 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1565 of SEQ ID NO:78, b is an integer of 15 to 1579, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:78, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 69

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 37 - 62 of the amino acid sequence referenced in Table 1 for this gene. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to Type Ia membrane proteins. The translation product of this gene was also determined to have a conserved peroxidase-I domain located at about amino acid position 15 - 25 of the amino acid sequence referenced in Table 1 for this gene.

Preferred polypeptides of the invention comprise the following amino acid sequence: TLSLLVSLHTV (SEQ ID NO: 423). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in the brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a

biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological diseases and disorders, a non-limiting example of which includes, epilepsy. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, cancerous, and/or wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in brain tissue indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may

show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:79 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1382 of SEQ ID NO:79, b is an integer of 15 to 1396, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:79, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 70

When tested against Jurkat cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates T-cells, and to a lesser extent, other cells and tissue cell-types, through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. Additional embodiments of the invention include polypeptides comprising the following amino acid sequences:

MSSSGTSDASPSGSPVLASYKPAPPKDKLPETPRRRMKKSLSAPLHPEFEEVYRFGAESRKLLLREPVD
AMPDPTPFLLARESAEVHLIKERPLVIPPIASDRSGEQHSPAREKPHKAHVGVAHRIHHATPPQPARGE
DPGGRPGERRQGGEEALRDGQNCVKPAVPHPALSMHCEHHWEISATPFLFNPMHAKHFSHLPTHSPSAS
LALFFTPKYDRVPAAEYVFPNCCGQTPVCRIACF (SEQ ID NO: 424); MSSSGTSDASPSGSPV
LASYKPAPPKDKLPETPRRRMKKSLSAPLHPEFEEVYRFGAESRKLLLREPVDAMPDPTPFLLARESAE
(SEQ ID NO: 425); VHLIKERPLVIPPIASDRSGEQHSPAREKPHKAHVGVAHRIHHATPPQPAR
GEDPGGRPGERR (SEQ ID NO: 426); QGGEEALRDGQNCVKPAVPHPALSMHCEHHWEISAT
PFLFNPMHAKHFSHLPTHSPSASLALFFTPKYDRVPAAEYVFPNCCGQTPVCRIACF (SEQ ID NO:

427); KRASQPPCTRNLKRSTDSGQRAGNSFCGNQWMLCPTPPHFCWLGSPPRSTSSKRGPSSS (SEQ ID NO: 428); and PPSPPTEAASSTARPAKSRTRPTSGWHIGSTTPPRRSQPEVKTLAV DQVNGGKVVRKHSGTDRTV (SEQ ID NO: 429). Additional embodiments are directed to polynucleotides encoding these polypeptides.

The gene encoding the disclosed cDNA is believed to reside on chromosome 12. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 12.

This gene is expressed primarily in Endometrial Tumor, fetal liver, Hypothalamus, Larynx carcinoma III, Prostate Cancer.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, endometrial tumor, larynx carcinoma III, prostate cancer, in addition to other proliferative diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive, hepatic, and pulmonary systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., hepatic, developmental, differentiating, proliferative, and cancerous, and/or other tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid, pulmonary surfactant) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 199 as residues: Ala-62 to Tyr-71. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in tumors of endometrium, larynx, and prostate origins, combined with the detected GAS biological activity, indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. The expression within cellular sources marked by proliferating cells indicates this protein

may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Alternatively, the tissue distribution within liver tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various would-healing models and/or tissue trauma. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:80 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1216 of SEQ ID NO:80, b is an integer of 15 to 1230, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:80, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 71

In another embodiment, polypeptides of the invention comprise the following amino acid sequence: MWNPNAGQPGPNPYPPNIGCPGGSNPAHPPPINPPFPPGPCPPPPGAPHGN

PAFPPGGPPHPVPQPGYPGCQPLGPYPPPYPPPAPGIPPVNPLAPGMVGPAVIVDKKMQKKMKKAHKKM
HKHQKHHKYHKHGKHSSSSSSSSSSDSD (SEQ ID NO: 430); RVGPDAWADAWEQAQAAVERLE
DTPKHVESQCRAARAKSISPQYWVPWRFQSCPPTTY (SEQ ID NO: 431); STLSPRPLSSSPR
SSPWQSSFPPRWAPSSCATARVSRMPTVGSLPSSIPTACPWNPSCESLGSWHGWTSSDSRQEDAEENEE
SS (SEQ ID NO: 432); MPGSQGQIHIPPILGALEVPILPTHHLLIHPFPQAPVLLPQELPMA
IQLSPQVGPLILCHSQGIQDANRWVPTLLHTHRLPLESLL (SEQ ID NO: 433); and/or
MASIPPLPPPLPAVILTEYRPWTLPSSLTSSALPSSFRCHVVLGECSPCAPHPLPXPEPHPAVEP
(SEQ ID NO: 434). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in bone marrow and primary dendritic cells, in addition to macrophages.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of immune and haematopoeitic diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., haematopoeitic, immune, and cancerous, and/or other tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid, and/or lymph) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in bone marrow indicates polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy,

immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:81 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1125 of SEQ ID NO:81, b is an integer of 15 to 1139, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:81, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 72

In another embodiment, polypeptides of the invention comprise the following amino acid sequence:

PRHTYWGIWLVPAAMASPHSHPAQGVLQPPGPQPRWEDRVALGTRGRSPGAYLTESAPQQASTTPGPPT CHGKVGSEWAWLGAAPGPLPTHPSHYAIRVPSNICSCPGASSAPALRGVVRQPPGPQNPRQGGRRGTRA SPVGSLFCV (SEQ ID NO: 435); MFAVLPAVEGRATPHQDRTCYPSRSRPWPSQPSPRGSM PVPRPGAARGQLDGHVQGQGWALQWGGPPAPAVYRRMALPPRAAGSYLDRKCPHPLPGARLCPGLPL (SEQ ID NO: 436); VFGAVFLTTPSHDLATPTGASGWCLLPWPAPTLTLHRGSCSPQAHSLVG RTGWPWGQEGGAQGLTSLRVLPSRHPLPQGPPHVMARLVVNGPGWEQPLAHCPPTHLTMQFEFQATFAP ALGPALPQP (SEQ ID NO: 437); HEEPPAGFGLRSLWRRSPPHEVGARLPNGAFGFSVRCLLCF PPWRAEPPHIRIGRATPPGPGPGPASPALEARCLCQGQGQPEGSWMATCRVKAGPCSGAGRQPQQFTDA WLFLPEQPAATWTGNVLIPSLGPGSALAFLCEPLLSLCCLGTPDRGVRVCPSVTFYSPRVEERKRGKSK GVQTPPQ (SEQ ID NO: 438); MATCRVKAGPCSGAGRQPQQFTDAWLFLPEQPAATWTGNVLIP SLGPGSALAFLCEPLLSLCCLGTPDRGVRVCPSVTFYSPRVEERKRGKSKGVQTPPQ (SEQ ID NO: 439); MKWFSTQPLWLNTKQRSHRRGPGPPPAPLSGVLGSRGLPHHPSQGWGRAGPRAGANVAWNSN

CIVRWVGGQWARGCSQPGPFTTNLAMTCGGPWGSGCLLGSTLSEVSPWAPPSCPQGHPVLPTRLWAWGL
QDPLCRVRVGAGHGSRHQPDAPVGVARSWDGVVRNTAPKTQNKNTTNGRRSPPPTEVGFEPLLIFPVSF
LQPLVSRKSQTGTHAHHGQESRDSTKKGGVHRGRPGQSLAPGRG (SEQ ID NO: 440); KVTDGH
TRTPRSGVPRQHKERRGSQRKARAEPGPREGMRTFPVQVAAGCSGRKSHASVNCWGWRPAPLQGPALTL
HVAIQLPSGCPWPWHRHRASRAGLAGPGPGPGGVARPILMWGGSALHGGKHSKHRTLKPKAPLGSLAPT
SWGGDRRHRDLSPKPAGGSSC (SEQ ID NO: 441); and/or MRTFPVQVAAGCSGRKSHASV
NCWGWRPAPLQGPALTLHVAIQLPSGCPWPWHRHRASRAGLAGPGPGPGGVARPILMWGGSALHGGKHS
KHRTLKPKAPLGSLAPTSWGGDRRHRDLSPKPAGGSSC (SEQ ID NO: 442).

Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome 7. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 7.

This gene is expressed primarily in healing wound tissues, macrophage-oxLDL, hemangiopericytoma, and CD34+ cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, healing wound, and proliferative diseases and/or disorders, particularly soft tissue cancers, such as hemangiopericytoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of healing wounds, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., lymph, cancerous, and/or wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid, and/or lymph) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 201 as residues: Met-1 to Gly-6, Arg-23 to Gly-33, Arg-60 to Ala-66, Thr-90 to Gly-103, Glu-105 to Trp-112. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution within healing wounds indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of cancer and other proliferative disorders. Representative uses are described elsewhere herein. Expression within cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division. Additionally, the expression in hematopoietic cells and tissues indicates that this protein may play a role in the proliferation, differentiation, and/or survival of hematopoietic cell lineages. In such an event, this gene is useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor cells. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:82 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1395 of SEQ ID NO:82, b is an integer of 15 to 1409, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:82, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 73

The translation product of this gene has homology to the Pro-Pol-dUTPase polyprotein of a newly discovered retrovirus. Since this protein also shares homology

to the human HERV-L element, and considering that most retroviruses integrate their proviral form into eukaryotic genomes through a homologous recombination mechanism, this gene is useful in providing protection against retroviral infections or could be used in the development of gene therapy applications (See Genebank Accession No.2065210; all references available through this accession are hereby incorporated by reference herein).

Preferred polypeptides of the invention comprise the following amino acid sequence: GLMECLIHRHGSH (SEQ ID NO: 443), and/or STKGMQFILTGITLSGY (SEQ ID NO: 444). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in CD34 positive cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune diseases and/or disorders, particularly viral infections. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, and cancerous, wounded, and/or other tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid, and/or lymph) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 202 as residues: Arg-39 to Thr-49, Leu-52 to Gly-60, Ser-67 to Arg-76, Gln-130 to Phe-137, Ser-139 to His-148. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in CD34+ immune cells combined with the homology to a retroviral protein indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in immune indicates a role in the regulation

of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer e.g. by boosting immune responses.

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:83 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 700 of SEQ ID NO:83, b is an integer of 15 to 714, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:83, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 74

The translation product of this gene shares sequence homology with mouse, bovine, and human butyrophilins, which are thought to be important in lactation especially during the latter part of pregnancy. Butyrophilin is a glycoprotein of the immunoglobulin superfamily that is secreted in association with the milk-fat-globule

membrane from mammary epithelial cells (See Genbank Accession No.gb|AAB51034.1, and Geneseq Accession No. W97814; all references available through these accessions are hereby incorporated herein by reference; for example, Mamm. Genome 7 (12), 900-905 (1996)). Based on the sequence similarity, The translation product of this gene is expected to share at least some biological activities with glycoproteins. Such activities are known in the art, some of which are described elsewhere herein.

In another embodiment, polypeptides of the invention comprise the following amino acid sequence: PRVRALLFARSLRLCRWGAKRLGVASTEAQRGVSFKLEEKTAHSSLALFRD DTGVKYGLVGLEPTKVALNVERFREWAVVLADTAVTSGRHYWEVTVKRSQQFRIGVADVDMSRDSCIGV DDRSWVFTMPSASGTPCWPTRKPQLRVLGSQEVGLLLEYEAQKLSLVDVSQVSVVHTLQTDFRGPVVPA FALWDGELLTHSGLEVPEGL (SEQ ID NO: 445), and/or MSRDSCIGVDDRSWVFTMPSASG TPCWPTRKPQLRVLGSQEVGLLLEYEAQKLSLVDVSQVSVVHTLQTDFRGPVVPAFALWDGELLTHSGL EVPEGL (SEQ ID NO: 446). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in adult heart, LNCAP cell line, OB cell line (HOS fraction), and epididymis, and to a lesser extent in a variety of other cells and tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, coronary disease and heart tumors and reproductive disorders, particularly those of the male reproductive system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly those of the heart and reproductive system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., cardiovascular, cardiac, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, seminal fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression

level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 203 as residues: Gly-30 to Ser-36. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution and homology to butyrophilin indicates that polynucleotides and polypeptides corresponding to this gene are useful for for determining the mechanisms underlying mammary-specific gene expression, lactation, and potentially for the production of copious amounts of butyrophilin or heterologous proteins in the milk of transgenic animals. The secreted protein can also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, and as nutritional supplements. It may also have a very wide range of biological activities. Representative uses are described in the "Chemotaxis" and "Binding Activity" sections below, in Examples 11, 12, 13, 14, 15, 16, 18, 19, and 20, and elsewhere herein. Briefly, the protein may possess the following activities: cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of hematopoiesis (e.g. for treating anemia or as adjunct to chemotherapy); stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors); hemostatic or thrombolytic activity (e.g. for treating hemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's disease); as antimicrobials; for treating psoriasis or other hyperproliferative diseases; for regulation of metabolism, and behavior. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies

directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:84 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1083 of SEQ ID NO:84, b is an integer of 15 to 1097, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:84, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 75

The translation product of this gene shares sequence homology with angiopoietin-2 which is thought to be important in regulation of angiogenesis through the Tie2, or other receptor tyrosine kinase (See Genbank Accession Nos. gb|AAC97965.1| (AF110520), and gb|AAB63189.1| (AF004326); in addition to Geneseq Accession No. R94603; all references available through these accessions are hereby incorporated herein by reference; for example, Science 277 (5322), 55-60 (1997)). Based on the sequence similarity, The translation product of this gene is expected to share at least some biological activities with angiogenic and kinase proteins. Such activities are known in the art, some of which are described elsewhere herein.

In another embodiment, polynucleotides of the invention comprise the following nucleic acid sequence:

GCACGAGCGGCACGAGCGGATCCTCACACGACTGTGATCCGATTCTTTCCAGCGGCTTCTGCAACCAAG
CGGGTCTTACCCCCGGTCCTCCGCGTCTCCAGTCCTCGCACCTGGAACCCCAACGTCCCCGAGAGTCCC
CGAATCCCCGCTCCCAGGCTACCTAAGAGGATGAGCGGTGCTCCGACGGCCGGGGCAGCCCTGATGCTC
TGCGCCGCCACCGCCGTGCTACTGAGCGCTCAGGGCGGACCCGTGCAGTCCAAGTCGCCGCGCTTTGCG
TCCTGGGACGAGATGAATGTCCTGGCGCACGGACTCCTGCAGCTCGGCCAGGGGCTGCGCGAACACGCG
GAGCGCACCCGCAGTCAGCTGAGCGCGCTGGAGCGGCGCCTGAGCGCGTGCGGGTCCGCCTGTCAGGGA
ACCGAGGGGTCCACCGACCTCCCGTTAGCCCCTGAGAGCCGGGTGGACCCTGAGGTCCTTCACAGCCTG

CAGACACAACTCAAGGCTCAGAACAGCAGGATCCAGCAACTCTTCCACAAGGTGGCCCAGCAGCAGCGG
CACCTGGAGAAGCAGCACCTGCGAATTCAGCATCTGCAAAGCCAGTTTGGCCTCCTGGACCACAAGCAC
CTAGACCATGAGGTGGCCAAGCCTGCCCGAAGAAAGAGGCTGCCCGAGATGGCCCAGCCAGTTGACCCG
GCTCACAATGTCAGCCGCCTGCACCGGCTGCCCAGGGATTGCCAGGAGCTGTTCCAGGTTGGGGAGAGG
CAGAGTGGACTATTTGAAATCCAGCCTCAGGGGTCTCCGCCATTTTTGGTGAACTGCAAGATGACCTCA
GATGGAGGCTGGACAGTAATTCAGAGGCGCCACGATGGCTCAGTGGACTTCAACCGGCCCTGGGAAGCC
TACAAGGCGGGGTTTGGGGATCCCCACGGCGAGTTCTGGCTGGGTCTGGAGAAGGTGCATAGCATCACG
GGGGACCGCAACAGCCGCCTGGCCGTGCAGCTGCGGGACTGGGATGGCAACGCCGAGTTGCTGCAGTTC
TCCGTGCACCTGGGTGGCGAGGACACGGCCTATAGCCTGCAGCTCACTGCACCCGTGGCCGGCCAGCTG
GGCGCCACCACCGTCCCACCCAGCGGCCTCTCCGTACCCTTCTCCACTTGGGACCAGGATCACGACCTC
CGCAGGGACAAGAACTGCGCCAAGAGCCTCTCTGGAGGCTGGTGGTTTGGCACCTGCAGCCATTCCAAC
CTCAACGGCCAGTACTTCCGCTCCATCCCACAGCAGCGGCAGAAGCTTAAGAAGGGAATCTTCTGGAAG
ACCTGGCGGGGCCGCTACTACCCGCTGCAGGCCACCACCATGTTGATCCAGCCCATGGCAGCAGAGGCA
GCCTCCTAGCGTCCTGGCTGGGCCTGGTCCCAGGCCCACGAAAGACGGTGACTCTTGGCTCTGCCCGAG
GATGTGGCCGTTCCCTGCCTGGGCAGGGGCTCCAAGGAGGGGCCATCTGGAAACTTGTGGACAGAGAAG
AAGACCACGACTGGAGAAGCCCCCTTTCTGAGTGCAGGGGGGCTGCATGCGTTGCCTCCTGAGATCGAG
GCTGCAGGATATGCTCAGACTCTAGAGGCGTGGACCAAGGGGCATGGAGCTTCACTCCTTGCTGGCCAG
GGAGTTGGGGACTCAGAGGGACCACTTGGGGCCAGCCAGACTGGCCTCAATGGCGGACTCAGTCACATT
GACTGACGGGGACCAGGGCTTGTGTGGGTCGAGAGCGCCCTCATGGTGCTGGTGCTGTTGTGTGTAGGT
CCCCTGGGGACACAAGCAGGCGCCAATGGTATCTGGGCGGAGCTCACAGAGTTCTTGGAATAAAAGCAA
CCTCAGAACAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA (SEQ ID NO: 447),
and/or
ATGAGCGGTGCTCCGACGGCCGGGGCAGCCCTGATGCTCTGCGCCGCCACCGCCGTGCTACTGAGCGCT
CAGGGCGGACCCGTGCAGTCCAAGTCGCCGCGCTTTGCGTCCTGGGACGAGATGAATGTCCTGGCGCAC
GGACTCCTGCAGCTCGGCCAGGGGCTGCGCGAACACGCGGAGCGCACCCGCAGTCAGCTGAGCGCGCTG
GAGCGGCGCCTGAGCGCGTGCGGGTCCGCCTGTCAGGGAACCGAGGGGTCCACCGACCTCCCGTTAGCC
CCTGAGAGCCGGGTGGACCCTGAGGTCCTTCACAGCCTGCAGACACAACTCAAGGCTCAGAACAGCAGG
ATCCAGCAACTCTTCCACAAGGTGGCCCAGCAGCAGCGGCACCTGGAGAAGCAGCACCTGCGAATTCAG
CATCTGCAAAGCCAGTTTGGCCTCCTGGACCACAAGCACCTAGACCATGAGGTGGCCAAGCCTGCCCGA
AGAAAGAGGCTGCCCGAGATGGCCCAGCCAGTTGACCCGGCTCACAATGTCAGCCGCCTGCACCGGCTG
CCCAGGGATTGCCAGGAGCTGTTCCAGGTTGGGGAGAGGCAGAGTGGACTATTTGAAATCCAGCCTCAG
GGGTCTCCGCCATTTTTGGTGAACTGCAAGATGACCTCAGATGGAGGCTGGACAGTAATTCAGAGGCGC
CACGATGGCTCAGTGGACTTCAACCGGCCCTGGGAAGCCTACAAGGCGGGGTTTGGGGATCCCCACGGC
GAGTTCTGGCTGGGTCTGGAGAAGGTGCATAGCATCACGGGGGGACCGCAACAGCCGCCTGGCCGTGCAG
CTGCGGGACTGGGATGGCAACGCCGAGTTGCTGCAGTTCTCCGTGCACCTGGGTGGCGAGGACACGGCC
TATAGCCTGCAGCTCACTGCACCCGTGGCCGGCCAGCTGGGCGCCACCACCGTCCCACCCAGCGGCCTC
TCCGTACCCTTCTCCACTTGGGACCAGGATCACGACCTCCGCAGGGACAAGAACTGCGCCAAGAGCCTC
TCTGGAGGCTGGTGGTTTGGCACCTGCAGCCATTCCAACCTCAACGGCCAGTACTTCCGCTCCATCCCA
CAGCAGCGGCAGAAGCTTAAGAAGGGAATCTTCTGGAAGACCTGGCGGGGCCGCTACTACCCGCTGCAG
GCCACCACCATGTTGATCCAGCCCATGGCAGCAGAGGCAGCCTCCTAG (SEQ ID NO: 448).

A preferred polypeptide fragment of the invention comprises the following amino acid sequence: MAQWTSTGPGKPTRRGLGIPTASSGWVWRRCIASWGTATAAWPCSCGTGMA TPSCCSSPCTWVARTRPIACSSLHPWPASWAPPPSHPAASPYPSPLGTRITTSAGTRTAPRASLEAGGL APAAIPTFNGPVLPAPSHSSGRSLRRESSGRPAGRYYPLQATTMLIQPMAAEAAS (SEQ ID NO: 449). Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome 19. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 19.

This gene is expressed primarily in oseteoarthritic tissues, kidney cortex, bone marrow, larynx carcinoma, and pineal gland, and to a lesser extent in placenta, stromal cells, epithelioid sarcoma, and a variety of other cells and tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, arthritis, kidney and urinary tract disorders, immune cell and system dysfunctions, disorders of the pineal gland and brain, and carcinomas, particularly of the larnyx. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly those of the immune, connective, endocrine, and urinary systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 204 as residues: Pro-27 to Arg-34, Glu-60 to Gln-65, Cys-80 to Thr-87, Leu-109 to Ile-116, Ala-124 to Gln-133, Lys-158 to Leu-165, Arg-229 to Ser-234, Asp-236 to Trp-241, Thr-266 to Ser-271, Thr-328 to Lys-343, Ser-355 to Tyr-363, Ile-367 to Lys-376, Thr-382 to Tyr-387. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution and homology to angiopoietin-2 indicates that polynucleotides and polypeptides corresponding to this gene are useful for the regulation of angiogenesis, particularly since angiogenesis is thought to depend on a precise balance of positive and negative regulation. Angiopoietin-1 (Ang1) is an angiogenic factor that signals through the endothelial cell-specific Tie2 receptor tyrosine kinase and, like vascular endothelial growth factor, is essential for normal vascular development in the mouse. Angiopoietin-2 is a naturally occurring antagonist for Angiopoietin-1 and Tie2. Transgenic overexpression of Angiopoietin-2 disrupts blood vessel formation in the mouse embryo. In adult mice and humans, Angiopoietin-2 is expressed only at sites of vascular remodeling. As such, this gene, or antagonists thereof, are useful in the diagnosis and treatment of arthritis, bone growth and remodeling, cancers (particularly those of bone, connective, lymphatic, and vascular tissues), ischaemia, lymphangiogenesis, lymphadnitis, lymphadenoma, lymphadenosis, lymphangitis, lymphangioendothelioma, lymphangioma, lymphangiophlebitis, lymphangiosarcom, lymphatitis, lymphedema, lymphenteritis, angioma, angiomegaly, amgiomyosarcoma, amgiomyoma, angiomyolipoma, angiomyoneuroma, angioneuromyoma, angiosarcoma, angiostenosis, angiotelectasis, and as a lymphagogue. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:85 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1917 of SEQ ID NO:85, b is an

integer of 15 to 1931, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:85, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 76

The translation product of this gene was shown to have homology to the DPM2 mannosyl transferase gene, which is known to be important in O-linked oligosaccaride glycosylation of proteins. Mutations within this gen have been shown to result in reduced levels of O-glycosylation. Since defects in proper protein glycosylation can result in the development of antigen-specific antibodies to such protein or altered pharmacokinetics (i.e., plasma half-life, in vivo clearance rate, etc.), the protein product of this gene may show utility in the treatment, diagnosis, and/or prevention of various abnormalities involving oligosaccaride metabolism, specifically those associated with O-glycosylation (See Genebank Accession No.R47201).

Preferred polypeptides of the invention comprise the following amino acid sequence: GHDLPQDAWLRWVLAGALCAGGWAVNYLPFFL (SEQ ID NO: 450), and/or FLYHYLPALTFQILLLPV (SEQ ID NO: 451). Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome 9. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 9.

This gene is expressed primarily in brain and melanocytes and to a lesser extent in breast, testis, and colon.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancers, particularly of the brain and melanocyte, in addition to neurological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, central nervous system, PNS, epithelial tissues including other parts of the integumentary system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types

(e.g., neural, cancerous and wounded tissues) or bodily fluids (e.g.lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 205 as residues: His-31 to Gln-38, Tyr-65 to Ser-71. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in brain tissue, combined with the homology to a known enzyme involved in oligosaccaride metabolism, indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:86 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1078 of SEQ ID NO:86, b is an integer of 15 to 1092, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:86, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 77

Preferred polypeptides of the invention comprise the following amino acid sequence: DICRLERAVCRDEPSALARALTWRQARAQAGA (SEQ ID NO: 453), XAPATXAW DTVVPPLPRKCQCSGSARSHGAGRSALHSPLEGSRPKVPAGAVGKSLPGQSRPQHCLPPKQPKQCRPGL ELKEGPLLTPTRASVQLSHPACLYWAPLLWIRDPASV (SEQ ID NO: 454), XAPATXAWDTVV PPLPRKCQCSGSARSHGAGRSALHSPLEGSRPKVPAGAVGKSL (SEQ ID NO: 455), PGQSRPQ HCLPPKQPKQCRPGLELKEGPLLTPTRASVQLSHPACLYWAPLLWIRDPASV (SEQ ID NO: 456), and/or MSPLPWPGPLPGGRQGHRLEPCCSSGCAGGPTWPHCSSQSWPMXSARHXGLGHC CPSSP (SEQ ID NO: 452). Polynucleotides encoding these polypeptides are also provided.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

DICRLERAVCRDEPSALARALTWRQARAQAGAMLLFGLCWGPYVATLLL SVLAYXQRPPLXPGTLLSLLSLGSASAAAVPVAMGLGDQRYTAPWRAAAQRCLQGLWGRASRDSPGPSI AYHPSSQSSVDLDLN (SEQ ID NO: 457). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in cells of the immune system, including dendritic cells and T cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a

biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders affecting the immune system, particularly immunodeficiencies such as AIDS. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in dendritic and T cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis,treatment and/or prevention of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Expression of this gene product in tonsils indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer e.g., by boosting immune responses.

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. Moreover, the protein may represent a secreted

factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissuemarkers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:87 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 564 of SEQ ID NO:87, b is an integer of 15 to 578, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:87, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 78

Preferred polypeptides of the invention comprise the following amino acid sequence: MERVGMESGEMVCGLGSACNNPSDLGQVPVPLWXSVSPPVFGXGWNGH (SEQ ID NO: 458), MRSFQDVSALEEWRGGKDLEPTHSLLLLLPLRDLLVVLGEIRKRQMEGCVWKGWGWNPEK WFAVLALPVTTRVTLGKSLSLSGXQFLHLYLERVGMGTEVLSSSDLL (SEQ ID NO: 459), MHPAGPTFMGSKPIREQQFGPDACLLLLCVAMAGTEASRAAQQCTSQKVRAGQDFSAHSNPXQIQVEKL XPREGQGLAQGHSGCYRQSQDRKPFLRIPSPPFPYTTLHLPFPDFAKNH (SEQ ID NO: 460), MHPAGPTFMGSKP IREQQFGPDACLLLLCVAMAGTEASRAAQQCTSQKVRAGQDFSAHSNP (SEQ ID NO: 461), PREGQGLAQGHSGCYRQSQDRKPFLRIPSPPFPYTTLHLPFPDFAKNH (SEQ ID NO: 462), DPRVRKPPTATLTTARTRPTTD (SEQ ID NO: 463), and/or AALEASVPAIATQRSSRQASGPNCCSLMGLDPMKVGPAGCISWDSVEADQVAGASGGRIEVKGCGMENL XRLHLGSGKGQXX (SEQ ID NO: 464). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in prostate and gall bladder.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders affecting the reproductive and gastrointestinal systems, including cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive and urogenital systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, bile, seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 207 as residues: Arg-21 to Glu-30. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in gall bladder indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, prevention, and/or treatment of various metabolic disorders such as Tay-Sachs disease, phenylkenonuria, galactosemia, porphyrias, and Hurler's syndrome. In addition, expression of this gene product in the prostate - while likely to be reflective of non-specific expression of a variety of genes in the testes - may nevertheless be indicative of a role for this gene product in normal prostate function, and may implicate this gene product in male fertility, and could even suggest its use as a male contraceptive. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:88 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 685 of SEQ ID NO:88, b is an integer of 15 to 699, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:88, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 79

Preferred polypeptides of the invention comprise the following amino acid sequence: GXANPEDSVCILEGFSVTALSILQHLVCHSGAVRLPITVRSGGRFCCWGRKQEPGSQ XSDGD (SEQ ID NO: 466), AVQQQHRVPQTAHCPPLLVGPWGSPCPPHCQPLSVQHHRERSDHL HITLAVGASDWGQGALAHQA (SEQ ID NO: 467), PKTLPVISCPGSSVCSKCCQSASAQRHPC LACCWLLSSSPCWRTTTSWHLSSVPTQKAASCCCCTCTSHHGLTEWPWRHNGSSWNKRWCGSWLSLVCK SPLPPVTGSNCQCNVEVVRALTVMLHRQWLTVRRAGGPPRTDQQRRTVRCLRDTVLLLHGLSQKDKLFM MHCVEVLHQFDQVMPGVSMLIRGLPDVTDCEEAALDDLCAAETDVEDPEVECG (SEQ ID NO: 468), and/or MLHRQWLTVRRAGGPPRTDQQRRTVRCLRDTVLLLHGLSQKDKLFMMHCVEVL HQFDQVMPGVSMLIRGLPDVTDCEEAALDDLCAAETDVEDPEVECG (SEQ ID NO: 465). Polynucleotides encoding these polypeptides are also provided.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

GXANPEDSVCILEGFSVTALSILQHLVCHSGAVRLPITVRSGGRFCCWGRK QEPGSQXSDGDMTSALRGVADDQGQHPLLKMLLHLLAFSSAATGHLQASVLTQCLKVLVKLAENTSCDF LPRFQCVFQVLPKCLSPETPLPSVLLAVELLSLLADHDQLAPQLCSHSEGCLLLLLYMYITSRPDRVAL ETQWLQLEQEVVWLLAKLGVQ EPLAPSHWLQLPV (SEQ ID NO: 469). Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome 3. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 3.

This gene is expressed primarily in breast, prostate, and to a lesser extent in testes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders affecting the reproductive organs of both males and females, especially cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, seminal fluid, breast milk, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution primarily in breast, prostate, and to a lesser extent in testes indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of disorders affecting the reproductive organs of males and females, including but not limited to cancers. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:89 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general

formula of a-b, where a is any integer between 1 to 1112 of SEQ ID NO:89, b is an integer of 15 to 1126, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:89, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 80

The translation product of this gene shares sequence homology with epsilon-COP which is part of coatomers which are thought to be important in maintaining Golgi structure and in mediating ER-through- Golgi transport, and which can influence normal endocytic recycling of LDL receptors (See Genebank Accession No. gi|2443869 (AC002985); all references available through this accession are hereby incorporated by reference herein).

Preferred polypeptides of the invention comprise the following amino acid sequence: MSGQLDARPAAALHPQGLAHPLWTCLLPRKGPSEVPQRPPQLWVVSISVLQGQHRGR AGPRDEQSVDVTNTTFLLMAASIYLHDQNPDAALRALHQGDSLEW (SEQ ID NO: 470), SVDVTNTTFLLMAASIYLHD (SEQ ID NO: 471), QNPDAALRALHQGDSLE (SEQ ID NO: 472), and/or RDSIVAELDREMSR (SEQ ID NO: 473). Polynucleotides encoding these polypeptides are also provided.

A preferred polypeptide fragment of the invention comprises the following amino acid sequence: MLGLLLLCTPRAWLTLSGPVCFQGRDPLRSHRGHPSCGS (SEQ ID NO: 474). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in breast tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders affecting the immune and reproductive systems, particularly of the mammary glands. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and reproductive systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, cancerous and wounded tissues) or bodily fluids (e.g., breast milk, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or

cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 209 as residues: Gly-24 to Gln-36, Gly-47 to His-66. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in breast tissue and homology to epsilon-COP indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of disorders affecting the immune and reproductive systems, including cancers, which arise from abnormalities in coatomer function, particularly of those tissues actively involved in secretory functions. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:90 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1023 of SEQ ID NO:90, b is an integer of 15 to 1037, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:90, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 81

The translation product of this gene shares sequence homology with the highly conserved epoxide hydrolase which is thought to have an important function in the catalysis of potentially toxic or carcinogenic epoxides into their corresponding, inert

diols (See e.g., Genbank Accession No. gi|485136; all references available through this accession are hereby incorporated by reference herein).

Preferred polypeptides of the invention comprise the following amino acid sequence: HGFPEFWYSWR (SEQ ID NO: 475), ASHWLQQDQP (SEQ ID NO: 476), PINHYRNIF (SEQ ID NO: 477), YPEMVMKLI (SEQ ID NO: 478), PEFWYSWRYQLREF (SEQ ID NO: 479), HDWGGMIAW (SEQ ID NO: 480). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in benign and malignant prostate tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the prostate and liver, particularly cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., hepatic, prostate, cancerous and wounded tissues) or bodily fluids (e.g., lymph, seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 210 as residues: Gln-38 to Pro-49, Glu-104 to Tyr-109, His-127 to Lys-132, Thr-236 to Cys-243, Gln-328 to Asp-333, Lys-344 to Asp-351. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in tumors of prostate origins indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional

supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Alternatively, homology to epoxide hydrolase indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of liver disorders and cancers (e.g., hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various would-healing models and/or tissue trauma.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:91 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1302 of SEQ ID NO:91, b is an integer of 15 to 1316, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:91, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 82

This gene is expressed primarily in merkel cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the immune system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g.immune, cancerous and wounded tissues) or bodily fluids (e.g.lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample

taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 211 as residues: Lys-23 to Lys-29. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in immune tissue indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer e.g. by boosting immune responses.

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:92 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1007 of SEQ ID NO:92, b is an

integer of 15 to 1021, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:92, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 83

This gene is expressed primarily in liver tissue, particularly hepatomas.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the liver, including cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hepatic and hematopoietic systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., hepatic, cancerous and wounded tissues) or bodily fluids (e.g., lymph, bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 212 as residues: Met-1 to Ser-7, His-66 to Phe-72. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in liver indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of liver disorders and cancers (e.g., hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various would-healing models and/or tissue trauma. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed

against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:93 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1246 of SEQ ID NO:93, b is an integer of 15 to 1260, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:93, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 84

Preferred polypeptides of the invention comprise the following amino acid sequence: GSLPPKPIYLVVPR (SEQ ID NO: 481). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in skin.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders affecting the skin, such as melanoma and wound healing, in addition to other disorders affecting the integumentary system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and skin, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., epithelial, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 213 as residues: Cys-56 to Pro-73, Pro-83 to Lys-92. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in skin and skin melanoma indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of various skin disorders including skin tumors, in addition to other tumors where expression has been indicated. Representative uses are described in the "Biological Activity", "Hyperproliferative Disorders", "Infectious Disease", and "Regeneration" sections below, in Example 11, 19, and 20, and elsewhere herein. Briefly, the protein is useful in detecting, treating, and/or preventing congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e. keratoses, Bowen's disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's disease, mycosis fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e.wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, uticaria, eczema, photosensitivity, autoimmune disorders (i.e., lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma. In addition, such disorders may predispose increased susceptibility to viral and bacterial infections of the skin (i.e., cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, althlete's foot, and ringworm). Moreover, the protein product of this gene may also be useful for the treatment or diagnosis of various connective tissue disorders (i.e., arthritis, trauma, tendonitis, chrondomalacia and inflammation, etc.), autoimmune disorders (i.e., rheumatoid arthritis, lupus, scleroderma, dermatomyositis, etc.), dwarfism, spinal deformation, joint abnormalities, amd chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:94 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 976 of SEQ ID NO:94, b is an integer of 15 to 990, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:94, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 85

When tested against kidney K562 cell lines, supernatants removed from cells containing this gene activated the interferon-sensitive responsive element (ISRE) pathway. Thus, it is likely that this gene activates kidney or endothelial cells through the ISRE signal transduction pathway. ISRE is a promoter element found upstream in many genes which are involved in the Jaks-STAT pathway. The Jaks-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. This gene maps to chromosome 10, and therefore, is used as a marker in linkage analysis for chromosome 10.

This gene is expressed primarily in placenta, and to a lesser extent in many other tissues or cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, vascular disease including occlusion of vessels and arteries. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the vascular system, expression of this gene at significantly higher or lower levels is routinely detected in

certain tissues or cell types (e.g., reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 214 as residues: His-58 to Gly-68, Thr-76 to Arg-81. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in placenta combined with the biological activity data indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of cancer and other proliferative disorders. Expression within highly vascularized tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division. Additionally, the expression in placenta indicates that this protein may play a role in the proliferation, differentiation, and/or survival of hematopoietic cell lineages. In such an event, this gene is useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor cells. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:95 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or

more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1696 of SEQ ID NO:95, b is an integer of 15 to 1710, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:95, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 86

This gene is Apolipoprotein M (See, e.g., Genbank Accession No. gb|AAD18084.1|(AF129756) and gb|AAD11443.1|(AF118393); all references available through these accessions are hereby incorporated by reference herein). The protein components of human lipoproteins, apolipoproteins, allow the redistribution of cholesterol from the arterial wall to other tissues and exert beneficial effects on systems involved in the development of arterial lesions, like inflammation and hemostasis.

The gene encoding the disclosed cDNA is believed to reside on chromosome 6. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 6.

This gene is expressed primarily in fetal liver, fetal spleen, and to a lesser extent in adult liver, hepatocellular tumors, retina and testis.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, proliferative disorders of the blood and tumors of the liver or disorders of lipid metabolism. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, metabolic, and hepatic systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., liver, hematopoietic, cancerous and wounded tissues) or bodily fluids (e.g., bile, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 215 as residues: Glu-106 to Lys-120, Glu-136 to Tyr-141, Asn-148 to Pro-154. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution of the gene product, ApoM, in fetal liver, and adult liver indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment and prevention of lipid metabolism disorders, including but not limited to, vascular disease, such as coronary artery disease, arteriosclerosis, and/or atherosclerosis Additionally, The tissue distribution in fetal liver and spleen indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product in fetal tissues indicates a role in regulating the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer e.g., by boosting immune responses.

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Alternatively, expression within liver tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of liver disorders and cancers (e.g.

hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various would-healing models and/or tissue trauma.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:96 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 767 of SEQ ID NO:96, b is an integer of 15 to 781, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:96, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 87

This gene is expressed primarily in LPS treated neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, chronic or acute inflammatory disease, and hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g.,hematopoietic, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in neutrophils indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency, etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:97 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1099 of SEQ ID NO:97, b is an integer of 15 to 1113, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:97, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 88

The translation product of this gene shares sequence homology with prolylcarboxypeptidase which is thought to be important in the processing of

bioactive peptides like angiotensin and bradykinin (See Genbank Accession No. gb|AAA99891.1|; all references available through this accession are hereby incorporated by reference herein).

Preferred polypeptides comprise the following amino acid sequence: LVFAEHRYYGKSLPFG (SEQ ID NO: 482), EQALADFAEL (SEQ ID NO: 483), GGSYGGMLSAYLRMKYPH (SEQ ID NO: 484), NIIFSNGNLDPWAGGG (SEQ ID NO: 485), AMMDYPYPTDFLGPLPANPVKV (SEQ ID NO: 486), and/or FYTGNEGD (SEQ ID NO: 487). Also preferred are the polynucleotides encoding these polypeptides. An additional preferred polypeptide fragment of the invention comprises the following amino acid sequence:

MGSAPWAPVLLLALGLRGLQAGARSGPRLPGALLPAASGPLQLRALRQQDL
PSALPGVGQVLGPGRGAHLLLHWERGRRVGLRQQLGLRRGLAAERGALLVFAEHRYYGKSLPFGAQSTQ
RGHTELLTVEQALADFAELLRALRRDLGAQDAPAIAFGGSYGGMLSAYLRMKYPHLVAGALAASAPVLS
VAGLGDSNQFFRDVTADFEGQSPKCTQGVREAFRQIKDLFLQGAYDTVRWEFGTCQPLSDEKDLTQLFM
FARNAFTVLAMMDYPYPTDFLGPLPANPVKVGCDRLLSEAQRITGLRALAGLVYNASGSEHCYDIYRLY
HSCADPTGCGTGPDARAWDYQACTEINLTFASNNVTDMFPDLPFTDELRQRYCLDTWGVWPRPDWLLTS
FWGGDLRAASNIIFSNGNLDPWAGGGIRRNLSASVIAVTIQGGAHHLDLRASHPEDPASVVEARKLEAT
IIGEWVKAARREQQPALRGGPRLSL (SEQ ID NO: 488). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in uterine cancer, testis, and to a lesser extent in lymph nodes, dendritic cells and HL60 cell line.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, uterine cancer, reproductive, and immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, seminal fluid, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,

the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 217 as residues: Gly-23 to Ala-30, Pro-44 to Phe-54, Glu-69 to Pro-77, Gln-142 to His-148, Phe-232 to Gly-242, Pro-271 to Leu-278, Ser-340 to Asp-347, Pro-365 to Asp-371, Asp-398 to Leu-406, Arg-500 to Pro-505. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in uterine cancer and homology to prolylcarboxypeptidase indicates that the protein product of this gene would is useful for diagnosis, treatment and prevention of diseases associated with the reproductive system including uterine cancer, as well as, cardiovascular diseases where prolylcarboxypeptidases primary substate, angiotension, has its greatest affect. In addition, the putative location of prolylcarboxypeptidase within the lysosomal compartment of cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, prevention, and/or treatment of various metabolic disorders such as Tay-Sachs disease, phenylkenonuria, galactosemia, porphyrias, and Hurler's syndrome. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:98 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1709 of SEQ ID NO:98, b is an integer of 15 to 1723, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:98, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 89

The translation product of this gene shares sequence homology with the human CGI-06 protein (See, e.g. Genbank Accession No. gb|AAD27715.1|AF132940_1 (AF132940); all references available through this accession are hereby incorporated by reference herein). When tested against the myeloid cell line, U937, supernatants removed from cells containing this gene activated the GAS (gamma activation site) pathway. Thus, it is likely that this gene activates myeloid cells through the Jaks-STAT signal transduction pathway. The GAS (gamma activation site) is a promoter element found upstream in many genes which are involved in the Jaks-STAT pathway. The Jaks-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

The gene encoding the disclosed cDNA is believed to reside on chromosome 20. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 20.

This gene is expressed primarily in various tumors including endometrial tumors, adenocarcinoma, breast cancer, osteosarcoma, chondrosarcoma, uterine and pancreas tumors and to a lesser extent in embryonic tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, identification and treatment of many types of solid tumors. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the major organs, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., skeletal, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., breast milk, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such

a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 218 as residues: Pro-25 to Arg-31, Thr-52 to Val-63, Asn-129 to Lys-135, Gln-197 to Trp-202, Thr-230 to Glu-236, Pro-242 to Tyr-248, Leu-280 to Pro-291, Ser-348 to Ser-356, Pro-362 to Gln-368, Thr-398 to His-406, Trp-430 to Leu-435, Glu-499 to Gly-504. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in solid tumors combined with the GAS-element activity indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of cancer and other proliferative disorders. Expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases.

The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Additionally, the expression in hematopoietic cells and tissues indicates

that this protein may play a role in the proliferation, differentiation, and/or survival of hematopoietic cell lineages. In such an event, this gene is useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor cells. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:99 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2073 of SEQ ID NO:99, b is an integer of 15 to 2087, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:99, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 90

This gene is expressed primarily in brain medulloblastoma cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of brain medulloblastoma and other neurological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, cancerous and wounded issues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an

individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in medulloblastoma indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:100 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 737 of SEQ ID NO:100, b is an integer of 15 to 751, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:100, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 91

This gene maps to the chromosome X, and therefore, is used as a marker in linkage analysis for chromosome X.

Preferred polypeptides of the invention comprise the following amino acid sequence: CSVFPPSLWFYLPLVFDDGDVQ (SEQ ID NO: 489), GVSLPLLGDASQLGYLGV RDALEEALCLFSDVQLCAGRTSALFKAXRQGRLSLQRILLPFVWLCPAPQRWSLQRQAGLLELRWAPPS SSFLAALFTPSSLGNGGRPSPSLTAXLQFDLRLLC (SEQ ID NO: 490), and/or VCRGFCC LLFGCALPPRGGVYRGRQASLNCGGLHRVRVSWPLCLPPQASAMVGA PPPASLPXCSLISDCCASNX (SEQ ID NO: 491). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in spleen from chronic lymphocytic leukemia patients.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, chronic lymphocytic leukemia, and other immune disorders, particularly proliferative diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in spleen from chronic lymphocytic leukemia patients indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product in leukemia cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or

other processes that may also suggest a usefulness in the treatment of cancer e.g., by boosting immune responses.

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:101 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1209 of SEQ ID NO:101, b is an integer of 15 to 1223, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:101, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 92

The translation product of this gene was shown to have homology to the human reverse transcriptase gene (See e.g., Genbank Accession No. gi|439877; all references available through this accession are hereby incorporated by reference herein).

Preferred polypeptides of the invention comprise the following amino acid sequence: MSHKHMRRSATSYIIRERQIKIIVRYHYTPIMTT (SEQ ID NO: 492), IRERQIK IIVRYHYTP (SEQ ID NO: 493), KKTCTMFIATLFT (SEQ ID NO: 494), SVASVFIP

LKVSVTKQFIFFXFFFFLRRSLAPAWVAERXTSQETKQNKKTPQLRGKVAHACDPITLGGRRWEVGESL EARSPS (SEQ ID NO: 496) and/or EKIFAKHLSVKGL (SEQ ID NO: 495). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in microvascular endothelial cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, various diseases of the cardiovascular and circulatory systems. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cardiovascular system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., vascular, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in microvascular endothelial cells combined with the homology to the conserved human gene for reverse transcriptase indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of cancer and other proliferative disorders, particularly vascular disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Alternatively expression within microvascular tissue, a tissue marked by proliferating cells, indicates that this protein may play a role in the regulation of cellular division. As such, this protein may play a role in the proliferation, differentiation, and/or survival of hematopoietic cell lineages. In such an event, this gene is useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor cells. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue

differentiation and could again be useful in cancer therapy. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:102 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 996 of SEQ ID NO:102, b is an integer of 15 to 1010, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:102, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 93

The translation product of this gene shares sequence homology with the Y43F4B.5 protein from Caenorhabditis elegans (See Genebank Accession No. gnl|PID|e1247424 (AL021481)). Moreover, the translation product also shares homology to phosphoglucomutase proteins (See Genbank Accession No. emb|CAA16334.1| (AL021481)). Based on the sequence similarity,The translation product of this gene is expected to share at least some biological activities with phosphoglucomutase proteins. Such activities are known in the art, some of which are described elsewhere herein.

Preferred polypeptides of the invention comprise the following amino acid sequence: ARGKTVLFAFEEAIGYMCCPFVLDKDGVSAAVISAELASFLATKNLSLSQQLKAIYVEYG YHITKASYFICHDQETIKKLFENLRNYDGKNNYPKACGKFEISAIRDLTTGYDDSQPDKKAVLPTSKSS QMITFTFANGGVATMRTSGTEPKIKYYAELCAPPGNSDPEQLKKELNELVSAIEEHFFQPQKYNLQPKA D (SEQ ID NO: 498), YMCCPFVLDKDGVSAAVISAELASFLATKNLSLSQQLKAIYVEYGYHIT KASYFICHDQETIKKLFENLRNYDGKNNYPKACGKFEISAIRDLTTGYDDSQPDKKAVLPTSKSSQMIT FTFANGGVATMRTSGTEPKIKYYAELCAPPGNSDPEQLKKELNELVSAIEEHFFQPQKYNLQPKAD

(SEQ ID NO:497), DKDGVSAAVISAELASFL (SEQ ID NO: 499), RDLTTGYDDSQPD (SEQ ID NO: 500), KAVLPTSKSSQMITF (SEQ ID NO: 501), and/or TMRTSGTEPKIKYYAEL (SEQ ID NO: 502). Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome 4. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 4.

This gene is expressed primarily in placenta, fetal spleen, and to a lesser extent in protate, T-cells and neutophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, various diseases of the immune and reproductive systems, including cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and reproductive systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., seminal fluid, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 222 as residues: Leu-23 to Met-30. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in fetal spleen indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or

activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Moreover, the protein is useful in the detection, treatment, and/or prevention of a variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, embolism, thrombosis, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:103 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or

more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1972 of SEQ ID NO:103, b is an integer of 15 to 1986, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:103, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 94

This gene is expressed primarily in activated monocytes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, various diseases and/or disorders of the immune system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in activated monocytes indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency

diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:104 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1319 of SEQ ID NO:104, b is an integer of 15 to 1333, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:104, and where b is greater than or equal to a + 14.

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
1	HWBBP10	209782 04/20/98	pCMVSport 3.0	11	899	1	899	66	66	130	1	26	27	56
1	HWBBP10	209782 04/20/98	pCMVSport 3.0	105	944	1	944	55	55	224	1	26	27	56
2	HWBDO80	209782 04/20/98	pCMVSport 3.0	12	1140	1	1140	166	166	131	1	22	23	41
3	HWHGU54	209782 04/20/98	pCMVSport 3.0	13	1445	1	1445	145	145	132	1	19	20	414
4	HYACI76	209782 04/20/98	pCMVSport 3.0	14	1208	1	1148	385	385	133	1	25	26	44
5	HBHMA23	209782 04/20/98	pSport1	15	1175	2	1175	71	71	134	1	24	25	197
5	HBHMA23	209782 04/20/98	pSport1	106	1172	1	1172	70	70	225	1	24	25	76
6	HCE3G20	209782 04/20/98	Uni-ZAP XR	16	2374	1	2350	57	57	135	1	42	43	45
7	HCEJP80	209782 04/20/98	Uni-ZAP XR	17	1595	1	1595	90	90	136	1	21	22	40
8	HCUDD24	209782 04/20/98	ZAP Express	18	1287	89	1287	314	314	137	1	19	20	84

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
9	HDPTD15	209782 04/20/98	pCMVSport 3.0	19	1396	1	1396	223	223	138	1	18	19	200
10	HDPWU34	209782 04/20/98	pCMVSport 3.0	20	1277	860	1277	117	117	139	1	23	24	325
10	HDPWU34	209782 04/20/98	pCMVSport 3.0	107	427	1	427	111	111	226	1	16	17	44
11	HEOOV79	209782 04/20/98	pSport1	21	1781	1	1767	203	203	140	1	23	24	118
12	HFKET93	209782 04/20/98	Uni-ZAP XR	22	1491	1	1491	75	75	141	1	15	16	47
13	HFTDL56	209782 04/20/98	Uni-ZAP XR	23	1839	32	1838	93	93	142	1	22	23	519
14	HFXJX44	209782 04/20/98	Lambda ZAP II	24	1384	1	1384	98	98	143	1	18	19	47
15	HKACU58	209782 04/20/98	pCMVSport 2.0	25	1681	1	1681	98	98	144	1	18	19	431
15	HKACU58	209782 04/20/98	pCMVSport 2.0	108	1708	69	1708	117	117	227	1	18	19	101
16	HKFBC53	209782 04/20/98	ZAP Express	26	1949	1	1906	41	41	145	1	18	19	442
16	HLDBQ19	209226 08/28/97	pCMVSport 3.0	109	1487	401	1487	534	534	228	1	22	23	132

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
16	HLDBQ19	97958 03/13/97	pCMVSport 3.0	110	1525	401	1480	534	534	229	1	22	23	66
17	HLTHR66	209782 04/20/98	Uni-ZAP XR	27	2286	1	2286	5	5	146	1	34	35	75
18	HLYBA69	209782 04/20/98	pSport1	28	530	1	530	89	89	147	1	29	30	51
19	HNTMX29	209782 04/20/98	pSport1	29	1296	756	1291	118	118	148	1	31	32	209
19	HNTMX29	209782 04/20/98	pSport1	111	552	1	552	18	18	230	1	18	19	72
20	HNTNC20	209782 04/20/98	pSport1	30	1979	1	1979	270	270	149	1	19	20	218
21	HNTNI01	209782 04/20/98	pSport1	31	1274	1	1114	306	306	150	1	33	34	49
22	HOHCK70	209782 04/20/98	pCMVSport 2.0	32	1531	1	1531	245	245	151	1	27	28	40
23	HSMBE69	209782 04/20/98	pSport1	33	2090	1	2090	69	69	152	1	18	19	107
24	HT4FW61	209782 04/20/98	Uni-ZAP XR	34	1006	31	1006	107	107	153	1	38	39	156
25	HYABK95	209782 04/20/98	pCMVSport 3.0	35	1787	1	1787	267	267	154	1	26	27	150

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
26	HYACE88	209782 04/20/98	pCMVSport 3.0	36	1201	1	1180	316	316	155	1	16	17	70
27	HOABR60	209782 04/20/98	Uni-ZAP XR	37	1896	1	903	45	45	156	1	16	17	490
27	HOABR60	209782 04/20/98	Uni-ZAP XR	112	925	1	903	45	45	231	1	16	17	293
28	HAGCT73	209782 04/20/98	Uni-ZAP XR	38	1152	1	1152	119	119	157	1	30	31	31
29	HAPOM45	209782 04/20/98	Uni-ZAP XR	39	1017	34	1017	98	98	158	1	31	32	115
30	HCEJQ69	209782 04/20/98	Uni-ZAP XR	40	1777	1	1777	39	39	159	1	26	27	380
31	HAGFI62	209782 04/20/98	Uni-ZAP XR	41	1003	368	992	429	429	160	1	28	29	91
32	HAGGS43	209782 04/20/98	Uni-ZAP XR	42	1201	1	1201	62	62	161	1	25	26	44
33	HBJHP03	209852 05/07/98	Uni-ZAP XR	43	1176	1	1176	185	185	162	1	20	21	45
34	HCHPF68	209852 05/07/98	pSport1	44	569	1	569	186	186	163	1	36	37	128
35	HDPJF37	209852 05/07/98	pCMVSport 3.0	45	986	1	986	196	196	164	1	23	24	57

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
36	HSDEZ20	209852 05/07/98	Uni-ZAP XR	46	1540	1	1540	66	66	165	1	41	42	97
37	HTEKU58	209852 05/07/98	Uni-ZAP XR	47	792	73	792	93	93	166	1	30	31	59
38	HLTBL58	209852 05/07/98	Uni-ZAP XR	48	1497	1	1497	26	26	167	1	20	21	42
39	HPWDJ42	209852 05/07/98	Uni-ZAP XR	49	1340	1	1340	149	149	168	1	18	19	54
39	HPWDJ42	209852 05/07/98	Uni-ZAP XR	113	1340	1	1340	149	149	232	1	21	22	54
39	HPWDJ42	209852 05/07/98	Uni-ZAP XR	114	813	1	813	161	161	233	1	18	19	47
40	HRACD15	209852 05/07/98	pCMVSport 3.0	50	1539	24	1539	252	252	169	1	40	41	53
40	HRACD15	209852 05/07/98	pCMVSport 3.0	115	1681	24	1453	252	252	234	1	40	41	53
41	HSIAC80	209852 05/07/98	Uni-ZAP XR	51	1423	1	1423	178	178	170	1	17	18	53
42	HAGFD18	209852 05/07/98	Uni-ZAP XR	52	1364	94	1364	261	261	171	1	21	22	48
43	HMTAT59	209852 05/07/98	pCMVSport 3.0	53	2288	501	2276	301	301	172	1	14	15	224

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
44	HDTGC86	209852 05/07/98	pCMVSport 2.0	54	1512	1	1512	351	351	173	1	27	28	200
45	HAGDI35	209852 05/07/98	Uni-ZAP XR	55	1357	1	1338	318	318	174	1	25	26	93
46	HELHN47	209852 05/07/98	Uni-ZAP XR	56	1989	883	1989	778	778	175	1	30	31	404
47	HPRBC80	209852 05/07/98	Uni-ZAP XR	57	2543	1245	2543	94	94	176	1	30	31	387
47	HPRBC80	209852 05/07/98	Uni-ZAP XR	116	2052	275	2032	404	404	235	1	26	27	69
48	HAQAR23	209852 05/07/98	Uni-ZAP XR	58	777	66	777	92	92	177	1	19	20	145
49	HAIFL18	209852 05/07/98	Uni-ZAP XR	59	879	1	879	274	274	178	1	29	30	140
50	HJPAY76	209852 05/07/98	Uni-ZAP XR	60	1161	1	1161	134	134	179	1	21	22	127
51	HUSXE77	209852 05/07/98	pSport1	61	687	1	687	156	156	180	1	20	21	146
52	HUFEF62	209852 05/07/98	pSport1	62	518	1	518	190	190	181	1	28	29	68
52	HUFEF62	209852 05/07/98	pSport1	117	539	1	539	182	182	236	1	28	29	68

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
53	HTWJK32	209852 05/07/98	Lambda ZAP II	63	911	211	911	376	376	182	1	20	21	51
54	HTWDF76	209852 05/07/98	pSport1	64	963	1	963	316	316	183	1	24	25	85
55	HTPBN68	209852 05/07/98	Uni-ZAP XR	65	1001	1	1001	429	429	184	1	20	21	191
56	HTOIY21	209852 05/07/98	Uni-ZAP XR	66	1558	1	1558	91	91	185	1	14	15	231
57	HTLDD53	209852 05/07/98	Uni-ZAP XR	67	1322	1	1322	162	162	186	1	25	26	68
58	HTLFG05	209852 05/07/98	Uni-ZAP XR	68	865	1	717	137	137	187	1	30	31	211
58	HTLFG05	209852 05/07/98	Uni-ZAP XR	118	882	1	882	137	137	237	1	30	31	67
59	HDPXR23	209852 05/07/98	pCMVSport 3.0	69	1150	20	1150	49	49	188	1	20	21	90
59	HDPXR23	209852 05/07/98	pCMVSport 3.0	119	1193	1	1189	95	95	238	1	20	21	90
60	HSIAC45	209852 05/07/98	Uni-ZAP XR	70	1398	1	1398	12	12	189	1	23	24	62
61	HSRGW16	209853 05/07/98	Uni-ZAP XR	71	1557	180	1007	72	72	190	1	12	13	295

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
61	HSRGW16	209853 05/07/98	Uni-ZAP XR	120	1338	1	1338	170	170	239	1	47	48	140
62	HSSJC35	209853 05/07/98	Uni-ZAP XR	72	1163	1	1163	55	55	191	1	30	31	295
62	HSSJC35	209853 05/07/98	Uni-ZAP XR	121	1183	1	1183	66	66	240	1	30	31	37
63	HTEAX23	209853 05/07/98	Uni-ZAP XR	73	1486	1	1486	72	72	192	1	20	21	338
64	HTGCH22	209853 05/07/98	Uni-ZAP XR	74	1553	1	1553	12	12	193	1	29	30	78
65	HTJMA95	209853 05/07/98	pCMVSport 2.0	75	1650	198	1569	527	527	194	1	22	23	181
66	HHEAA08	209853 05/07/98	pCMVSport 3.0	76	2150	1	2150	88	88	195	1	38	39	79
66	HHEAA08	209853 05/07/98	pCMVSport 3.0	122	615	1	615		311	241	1			20
67	HBQAA49	209853 05/07/98	Lambda ZAP II	77	1592	1	1592	197	197	196	1	37	38	69
68	HDPBI32	209853 05/07/98	pCMVSport 3.0	78	1579	598	1184	103	103	197	1	30	31	271
68	HDPBI32	209853 05/07/98	pCMVSport 3.0	123	587	1	587	51	51	242	1	35	36	138

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
69	HBIBF16	209853 05/07/98	Uni-ZAP XR	79	1396	1	1396	15	15	198	1	35	36	51
70	HBCAY05	209853 05/07/98	Uni-ZAP XR	80	1230	576	1209	627	627	199	1	22	23	71
71	HCUCK44	209853 05/07/98	ZAP Express	81	1139	573	1133	593	593	200	1	30	31	60
72	HCE2W56	209853 05/07/98	Uni-ZAP XR	82	1409	1	1409	61	61	201	1	21	22	143
73	HCWAG01	209853 05/07/98	ZAP Express	83	714	1	714	192	192	202	1	25	26	148
74	HLDBY02	209853 05/07/98	pCMVSport 3.0	84	1097	1	1097	326	326	203	1	30	31	36
75	HDRMI82	209853 05/07/98	pSport1	85	1931	540	1900	170	170	204	1	25	26	406
75	HDRMI82	209853 05/07/98	pSport1	124	1379	1	1357	328	328	243	1	30	31	175
76	HEPCU48	209853 05/07/98	Uni-ZAP XR	86	1092	1	1092	98	98	205	1	26	27	91
77	HDPRK33	209853 05/07/98	pCMVSport 3.0	87	578	1	573	99	99	206	1	44	45	101
78	HKGAX42	209853 05/07/98	pSport1	88	699	1	699	69	69	207	1	18	19	50

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
79	HLMAZ95	209853 05/07/98	Uni-ZAP XR	89	1126	7	1126	187	187	208	1	33	34	161
80	HLMFC07	209853 05/07/98	Lambda ZAP II	90	1037	1	1037	203	203	209	1	17	18	227
80	HLMFC07	209853 05/07/98	Lambda ZAP II	125	1268	1	1268	203	203	244	1	30	31	39
81	HL2AG87	209853 05/07/98	Uni-ZAP XR	91	1316	1	1316	110	110	210	1	37	38	351
82	HKGCO27	209853 05/07/98	pSport1	92	1021	1	1021	313	313	211	1	26	27	93
82	HKGCO27	209853 05/07/98	pSport1	126	1311	1	1311	57	57	245	1	26	27	47
83	HLDCE79	209853 05/07/98	pCMVSport 3.0	93	1260	1	1260	342	342	212	1	63	64	101
83	HLDCE79	209853 05/07/98	pCMVSport 3.0	127	1249	1	1249	298	298	246	1	30	31	34
84	HERAD40	209853 05/07/98	Uni-ZAP XR	94	990	1	990	85	85	213	1	38	39	98
85	HFOXB55	209853 05/07/98	pSport1	95	1710	1	1710	138	138	214	1	34	35	81
86	HFVGZ42	209853 05/07/98	pBluescript	96	781	1	781	71	71	215	1	22	23	188

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
87	HNHAF39	209853 05/07/98	Uni-ZAP XR	97	1113	1	1113	332	332	216	1	30	31	44
88	HNTSW57	209853 05/07/98	pSport1	98	1723	181	1723	19	19	217	1	21	22	515
88	HNTSW57	209853 05/07/98	pSport1	128	1660	1	1660	38	38	247	1	21	22	490
89	HOGCK20	209853 05/07/98	pCMVSport 2.0	99	2087	1	2087	57	57	218	1	23	24	522
89	HOGCK20	209853 05/07/98	pCMVSport 2.0	129	2075	1	2054		53	248	1	22	23	554
90	HMDAL49	209853 05/07/98	Uni-ZAP XR	100	751	1	751	52	52	219	1	22	23	52
91	HLYES38	209853 05/07/98	pSport1	101	1223	1	1223	69	69	220	1	22	23	73
92	HMECK83	209853 05/07/98	Lambda ZAP II	102	1010	1	1010	50	50	221	1	28	29	54
93	HSHAX21	209853 05/07/98	Uni-ZAP XR	103	1986	1	1986	177	177	222	1	13	14	72
94	HMQAG66	209853 05/07/98	Uni-ZAP XR	104	1333	1	1333	657	657	223	1	24	25	69

Table 1 summarizes the information corresponding to each "Gene No." described above. The nucleotide sequence identified as "NT SEQ ID NO:X" was assembled from partially homologous ("overlapping") sequences obtained from the "cDNA clone ID" identified in Table 1 and, in some cases, from additional related DNA clones. The overlapping sequences were assembled into a single contiguous sequence of high redundancy (usually three to five overlapping sequences at each nucleotide position), resulting in a final sequence identified as SEQ ID NO:X.

The cDNA Clone ID was deposited on the date and given the corresponding deposit number listed in "ATCC Deposit No:Z and Date." Some of the deposits contain multiple different clones corresponding to the same gene. "Vector" refers to the type of vector contained in the cDNA Clone ID.

"Total NT Seq." refers to the total number of nucleotides in the contig identified by "Gene No." The deposited clone may contain all or most of these sequences, reflected by the nucleotide position indicated as "5' NT of Clone Seq." and the "3' NT of Clone Seq." of SEQ ID NO:X. The nucleotide position of SEQ ID NO:X of the putative start codon (methionine) is identified as "5' NT of Start Codon." Similarly , the nucleotide position of SEQ ID NO:X of the predicted signal sequence is identified as "5' NT of First AA of Signal Pep."

The translated amino acid sequence, beginning with the methionine, is identified as "AA SEQ ID NO:Y," although other reading frames can also be easily translated using known molecular biology techniques. The polypeptides produced by these alternative open reading frames are specifically contemplated by the present invention.

The first and last amino acid position of SEQ ID NO:Y of the predicted signal peptide is identified as "First AA of Sig Pep" and "Last AA of Sig Pep." The predicted first amino acid position of SEQ ID NO:Y of the secreted portion is identified as "Predicted First AA of Secreted Portion." Finally, the amino acid position of SEQ ID NO:Y of the last amino acid in the open reading frame is identified as "Last AA of ORF."

SEQ ID NO:X and the translated SEQ ID NO:Y are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, SEQ ID NO:X is useful for designing nucleic acid hybridization

probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in the deposited clone. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y may be used to generate antibodies which bind specifically to the secreted proteins encoded by the cDNA clones identified in Table 1.

Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X and the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing a human cDNA of the invention deposited with the ATCC, as set forth in Table 1. The nucleotide sequence of each deposited clone can readily be determined by sequencing the deposited clone in accordance with known methods. The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular clone can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, or the deposited clone. The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

Also provided in the present invention are species homologs. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for the desired homologue.

The polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below). It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification , such as multiple histidine residues, or an additional sequence for stability during recombinant production.

The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified by the one-step method described in Smith and Johnson, Gene 67:31-40 (1988). Polypeptides of the invention also can be purified from natural or recombinant sources using antibodies of the invention raised against the secreted protein in methods which are well known in the art.

Signal Sequences

Methods for predicting whether a protein has a signal sequence, as well as the cleavage point for that sequence, are available. For instance, the method of McGeoch, Virus Res. 3:271-286 (1985), uses the information from a short N-terminal charged region and a subsequent uncharged region of the complete (uncleaved) protein. The method of von Heinje, Nucleic Acids Res. 14:4683-4690 (1986) uses the information from the residues surrounding the cleavage site, typically residues -13 to +2, where +1 indicates the amino terminus of the secreted protein. The accuracy of predicting the cleavage points of known mammalian secretory proteins for each of

these methods is in the range of 75-80%. (von Heinje, supra.) However, the two methods do not always produce the same predicted cleavage point(s) for a given protein..

In the present case, the deduced amino acid sequence of the secreted polypeptide was analyzed by a computer program called SignalP (Henrik Nielsen et al., Protein Engineering 10:1-6 (1997)), which predicts the cellular location of a protein based on the amino acid sequence. As part of this computational prediction of localization, the methods of McGeoch and von Heinje are incorporated. The analysis of the amino acid sequences of the secreted proteins described herein by this program provided the results shown in Table 1.

As one of ordinary skill would appreciate, however, cleavage sites sometimes vary from organism to organism and cannot be predicted with absolute certainty. Accordingly, the present invention provides secreted polypeptides having a sequence shown in SEQ ID NO:Y which have an N-terminus beginning within 5 residues (i.e., + or - 5 residues) of the predicted cleavage point. Similarly, it is also recognized that in some cases, cleavage of the signal sequence from a secreted protein is not entirely uniform, resulting in more than one secreted species. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

Moreover, the signal sequence identified by the above analysis may not necessarily predict the naturally occurring signal sequence. For example, the naturally occurring signal sequence may be further upstream from the predicted signal sequence. However, it is likely that the predicted signal sequence will be capable of directing the secreted protein to the ER. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

Polynucleotide and Polypeptide Variants

"Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

By a polynucleotide having a nucleotide sequence at least, for example, 95%

"identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the polynucleotide is identical to the reference sequence except that the polynucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a polynucleotide having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be an entire sequence shown inTable 1, the ORF (open reading frame), or any fragement specified as described herein.

As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the presence invention can be determined conventionally using known computer programs. A preferred method for determing the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. (1990) 6:237-245). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identiy are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the lenght of the subject nucleotide sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence

that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignement of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequnce are manually corrected for. No other manual corrections are to made for the purposes of the present invention.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid.

These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequences shown in Table 1 or to the amino acid sequence encoded by deposited DNA clone can be determined conventionally using known computer programs. A preferred method for determing the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. (1990) 6:237-245). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is becuase the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and

C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence.

For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C-termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequnce are manually corrected for. No other manual corrections are to made for the purposes of the present invention.

The variants may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, variants in which 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as E. coli).

Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an

organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level. Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the secreted protein without substantial loss of biological function. The authors of Ron et al., J. Biol. Chem. 268: 2984-2988 (1993), reported variant KGF proteins having heparin binding activity even after deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., J. Biotechnology 7:199-216 (1988).)

Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (J. Biol. Chem 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." (See, Abstract.) In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic

activities can readily be determined by routine methods described herein and otherwise known in the art.

Thus, the invention further includes polypeptide variants which show substantial biological activity. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as have little effect on activity. For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie, J. U. et al., Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. (Cunningham and Wells, Science 244:1081-1085 (1989).) The resulting mutant molecules can then be tested for biological activity.

As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of

the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly.

Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more of amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as an IgG Fc fusion region peptide, or leader or secretory sequence, or a sequence facilitating purification. Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).)

A further embodiment of the invention relates to a polypeptide which comprises the amino acid sequence of the present invention having an amino acid sequence which contains at least one amino acid substitution, but not more than 50 amino acid substitutions, even more preferably, not more than 40 amino acid substitutions, still more preferably, not more than 30 amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions. Of course, in order of ever-increasing preference, it is highly preferable for a polypeptide to have an amino acid sequence which comprises the amino acid sequence of the present invention, which contains at least one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions. In specific embodiments, the number of additions, substitutions, and/or deletions in the amino acid sequence of the present invention or fragments thereof (e.g., the mature form and/or other fragments described herein), is

1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, conservative amino acid substitutions are preferable.

Polynucleotide and Polypeptide Fragments

In the present invention, a "polynucleotide fragment" refers to a short polynucleotide having a nucleic acid sequence contained in the deposited clone or shown in SEQ ID NO:X. The short nucleotide fragments are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from the cDNA sequence contained in the deposited clone or the nucleotide sequence shown in SEQ ID NO:X. These nucleotide fragments are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., 50, 150, 500, 600, 2000 nucleotides) are preferred.

Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments having a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, or 2001 to the end of SEQ ID NO:X or the cDNA contained in the deposited clone. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has biological activity. More preferably, these polynucleotides can be used as probes or primers as discussed herein.

In the present invention, a "polypeptide fragment" refers to a short amino acid sequence contained in SEQ ID NO:Y or encoded by the cDNA contained in the deposited clone. Protein fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the

invention, include, for example, fragments from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, or 161 to the end of the coding region. Moreover, polypeptide fragments can be about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes.

Preferred polypeptide fragments include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred. Similarly, polynucleotide fragments encoding these polypeptide fragments are also preferred.

Also preferred are polypeptide and polynucleotide fragments characterized by structural or functional domains, such as fragments that comprise alpha-helix and alpha-helix forming regions, beta-sheet and beta-sheet-forming regions, turn and turn-forming regions, coil and coil-forming regions, hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions, substrate binding region, and high antigenic index regions. Polypeptide fragments of SEQ ID NO:Y falling within conserved domains are specifically contemplated by the present invention. Moreover, polynucleotide fragments encoding these domains are also contemplated.

Other preferred fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

Epitopes & Antibodies

In the present invention, "epitopes" refer to polypeptide fragments having antigenic or immunogenic activity in an animal, especially in a human. A preferred embodiment of the present invention relates to a polypeptide fragment comprising an epitope, as well as the polynucleotide encoding this fragment. A region of a protein molecule to which an antibody can bind is defined as an "antigenic epitope." In contrast, an "immunogenic epitope" is defined as a part of a protein that elicits an antibody response. (See, for instance, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998- 4002 (1983).)

Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985) further described in U.S. Patent No. 4,631,211.)

In the present invention, antigenic epitopes preferably contain a sequence of at least seven, more preferably at least nine, and most preferably between about 15 to about 30 amino acids. Antigenic epitopes are useful to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe, J. G. et al., Science 219:660-666 (1983).)

Similarly, immunogenic epitopes can be used to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., supra; Wilson et al., supra; Chow, M. et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle, F. J. et al., J. Gen. Virol. 66:2347-2354 (1985).) A preferred immunogenic epitope includes the secreted protein. The immunogenic epitopes may be presented together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse) or, if it is long enough (at least about 25 amino acids), without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting.)

As used herein, the term "antibody" (Ab) or "monoclonal antibody" (Mab) is meant to include intact molecules as well as antibody fragments (such as, for example, Fab and F(ab')2 fragments) which are capable of specifically binding to protein. Fab and F(ab')2 fragments lack the Fc fragment of intact antibody, clear more rapidly from the circulation, and may have less non-specific tissue binding than an intact antibody. (Wahl et al., J. Nucl. Med. 24:316-325 (1983).) Thus, these

fragments are preferred, as well as the products of a FAB or other immunoglobulin expression library. Moreover, antibodies of the present invention include chimeric, single chain, and humanized antibodies.

Fusion Proteins

Any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, the polypeptides of the present invention can be used as targeting molecules once fused to other proteins.

Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

Moreover, polypeptides of the present invention, including fragments, and specifically epitopes, can be combined with parts of the constant domain of immunoglobulins (IgG), resulting in chimeric polypeptides. These fusion proteins facilitate purification and show an increased half-life in vivo. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP A 394,827; Traunecker et al., Nature 331:84-86 (1988).) Fusion proteins having disulfide-linked dimeric structures (due to the

IgG) can also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., J. Biochem. 270:3958-3964 (1995).)

Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP-A 0232 262.) Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, D. Bennett et al., J. Molecular Recognition 8:52-58 (1995); K. Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).)

Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a peptide which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. (Wilson et al., Cell 37:767 (1984).)

Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

Vectors, Host Cells, and Protein Production

The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral

vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

The polynucleotides may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the E. coli lac, trp, phoA and tac promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance genes for culturing in E. coli and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as E. coli, Streptomyces and Salmonella typhimurium cells; fungal cells, such as yeast cells; insect cells such as Drosophila S2 and Spodoptera Sf9 cells; animal cells such as CHO, COS, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1

and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Other suitable vectors will be readily apparent to the skilled artisan.

Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., Basic Methods In Molecular Biology (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

A polypeptide of this invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

Polypeptides of the present invention, and preferably the secreted form, can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with the polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

Uses of the Polynucleotides

Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

The polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each polynucleotide of the present invention can be used as a chromosome marker.

Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp) from the sequences shown in SEQ ID NO:X. Primers can be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids

containing the human gene corresponding to the SEQ ID NO:X will yield an amplified fragment.

Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, and preselection by hybridization to construct chromosome specific-cDNA libraries.

Precise chromosomal location of the polynucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes). Preferred polynucleotides correspond to the noncoding regions of the cDNAs because the coding sequences are more likely conserved within gene families, thus increasing the chance of cross hybridization during chromosomal mapping.

Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library) .) Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease could be one of 50-500 potential causative genes.

Thus, once coinheritance is established, differences in the polynucleotide and the corresponding gene between affected and unaffected individuals can be examined. First, visible structural alterations in the chromosomes, such as deletions or

translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using polynucleotides of the present invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

In addition to the foregoing, a polynucleotide can be used to control gene expression through triple helix formation or antisense DNA or RNA. Both methods rely on binding of the polynucleotide to DNA or RNA. For these techniques, preferred polynucleotides are usually 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques are effective in model systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat disease.

Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell.

The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identifying personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a unique set of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erlich, H., PCR Technology, Freeman and Co. (1992).) Once these specific polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers specific to particular tissue prepared from the sequences of the

present invention. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue cultures for contamination.

In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

Uses of the Polypeptides

Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

A polypeptide of the present invention can be used to assay protein levels in a biological sample using antibody-based techniques. For example, protein expression in tissues can be studied with classical immunohistological methods. (Jalkanen, M., et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell . Biol. 105:3087-3096 (1987).) Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine (125I, 121I), carbon (14C), sulfur (35S), tritium (3H), indium (112In), and technetium (99mTc), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

In addition to assaying secreted protein levels in a biological sample, proteins can also be detected in vivo by imaging. Antibody labels or markers for in vivo imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as

deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, 131I, 112In, 99mTc), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously, or intraperitoneally) into the mammal. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of 99mTc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).)

Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression of a polypeptide of the present invention in cells or body fluid of an individual; (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a disorder.

Moreover, polypeptides of the present invention can be used to treat disease. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B), to inhibit the activity of a polypeptide (e.g., an oncogene), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth).

Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat disease. For example, administration of an antibody directed to a polypeptide of the present invention can bind and reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the following biological activities.

Biological Activities

The polynucleotides and polypeptides of the present invention can be used in assays to test for one or more biological activities. If these polynucleotides and polypeptides do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides could be used to treat the associated disease.

Immune Activity

A polypeptide or polynucleotide of the present invention may be useful in treating deficiencies or disorders of the immune system, by activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune deficiencies or disorders may be genetic, somatic, such as cancer or some autoimmune disorders, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, a polynucleotide or polypeptide of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

A polynucleotide or polypeptide of the present invention may be useful in treating or detecting deficiencies or disorders of hematopoietic cells. A polypeptide or polynucleotide of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat those disorders associated with a decrease in certain (or many) types hematopoietic cells. Examples of immunologic deficiency syndromes include, but are not limited to: blood protein disorders (e.g. agammaglobulinemia, dysgammaglobulinemia), ataxia telangiectasia, common variable immunodeficiency, Digeorge Syndrome, HIV infection, HTLV-BLV infection, leukocyte adhesion deficiency syndrome, lymphopenia, phagocyte bactericidal dysfunction, severe combined immunodeficiency (SCIDs), Wiskott-Aldrich Disorder, anemia, thrombocytopenia, or hemoglobinuria.

Moreover, a polypeptide or polynucleotide of the present invention could also be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (clot formation). For example, by increasing hemostatic or thrombolytic activity, a polynucleotide or polypeptide of the present invention could be used to treat blood coagulation disorders (e.g., afibrinogenemia, factor deficiencies), blood platelet disorders (e.g. thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, a polynucleotide or polypeptide of the present invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment of heart attacks (infarction), strokes, or scarring.

A polynucleotide or polypeptide of the present invention may also be useful in treating or detecting autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of a polypeptide or polynucleotide of the present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

Examples of autoimmune disorders that can be treated or detected by the present invention include, but are not limited to: Addison's Disease, hemolytic

anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitis, and autoimmune inflammatory eye disease.

Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated by a polypeptide or polynucleotide of the present invention. Moreover, these molecules can be used to treat anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

A polynucleotide or polypeptide of the present invention may also be used to treat and/or prevent organ rejection or graft-versus-host disease (GVHD). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The administration of a polypeptide or polynucleotide of the present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD.

Similarly, a polypeptide or polynucleotide of the present invention may also be used to modulate inflammation. For example, the polypeptide or polynucleotide may inhibit the proliferation and differentiation of cells involved in an inflammatory response. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., TNF or IL-1.)

Hyperproliferative Disorders

A polypeptide or polynucleotide can be used to treat or detect hyperproliferative disorders, including neoplasms. A polypeptide or polynucleotide of the present invention may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, a polypeptide or polynucleotide of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

Examples of hyperproliferative disorders that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but are not limited to neoplasms located in the: abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Similarly, other hyperproliferative disorders can also be treated or detected by a polynucleotide or polypeptide of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstron's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

Infectious Disease

A polypeptide or polynucleotide of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response.

Alternatively, the polypeptide or polynucleotide of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide of the present invention. Examples of viruses, include, but are not limited to the following DNA and RNA viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza), Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiollitis, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox , hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but not limited to, the following Gram-Negative and Gram-positive bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Norcardia), Aspergillosis, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceae, Blastomycosis, Bordetella, Borrelia, Brucellosis, Candidiasis, Campylobacter, Coccidioidomycosis, Cryptococcosis, Dermatocycoses, Enterobacteriaceae (Klebsiella, Salmonella, Serratia, Yersinia), Erysipelothrix, Helicobacter, Legionellosis, Leptospirosis, Listeria, Mycoplasmatales, Neisseriaceae (e.g., Acinetobacter, Gonorrhea, Menigococcal), Pasteurellacea Infections (e.g., Actinobacillus, Heamophilus, Pasteurella), Pseudomonas, Rickettsiaceae,

Chlamydiaceae, Syphilis, and Staphylococcal. These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea, meningitis, Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Moreover, parasitic agents causing disease or symptoms that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but not limited to, the following families: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas. These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), Malaria, pregnancy complications, and toxoplasmosis. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Preferably, treatment using a polypeptide or polynucleotide of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

Regeneration

A polynucleotide or polypeptide of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997).) The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteocarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

Moreover, a polynucleotide or polypeptide of the present invention may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. A polynucleotide or polypeptide of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

Similarly, nerve and brain tissue could also be regenerated by using a polynucleotide or polypeptide of the present invention to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stoke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotide or polypeptide of the present invention.

Chemotaxis

A polynucleotide or polypeptide of the present invention may have chemotaxis activity. A chemotaxic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

A polynucleotide or polypeptide of the present invention may increase chemotaxic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotaxic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

It is also contemplated that a polynucleotide or polypeptide of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, a polynucleotide or polypeptide of the present invention could be used as an inhibitor of chemotaxis.

Binding Activity

A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors),or small molecules.

Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991).) Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable

of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide, either as a secreted protein or on the cell membrane. Preferred cells include cells from mammals, yeast, Drosophila, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptide from suitably manipulated cells or tissues.

Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a

candidate binding compound with a polypeptide of the invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with a polypeptide of the invention, (b) assaying a biological activity , and (b) determining if a biological activity of the polypeptide has been altered.

Other Activities

A polypeptide or polynucleotide of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

A polypeptide or polynucleotide of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, a polypeptide or polynucleotide of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

A polypeptide or polynucleotide of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, caricadic rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

A polypeptide or polynucleotide of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

Other Preferred Embodiments

Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95%

identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Clone Sequence and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Start Codon and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Similarly preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:X beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X.

Also preferred is an isolated nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

Also preferred is a composition of matter comprising a DNA molecule which comprises a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the material deposited with the American Type Culture Collection and given the ATCC Deposit Number shown in Table 1 for said cDNA Clone Identifier.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the deposit given the ATCC Deposit Number shown in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least 50 contiguous nucleotides is included in the nucleotide sequence of the complete open reading frame sequence encoded by said human cDNA clone.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence selected from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

The method for identifying the species, tissue or cell type of a biological sample can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least

one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

The method for diagnosing a pathological condition can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1.

Also preferred is a polypeptide, wherein said sequence of contiguous amino acids is included in the amino acid sequence of SEQ ID NO:Y in the range of

positions beginning with the residue at about the position of the First Amino Acid of the Secreted Portion and ending with the residue at about the Last Amino Acid of the Open Reading Frame as set forth for SEQ ID NO:Y in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a secreted portion of the secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA

clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

Also preferred is an isolated nucleic acid molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a secreted portion of a human secreted protein comprising an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y beginning with the residue at the position of the First Amino Acid of

the Secreted Portion of SEQ ID NO:Y wherein Y is an integer set forth in Table 1 and said position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y is defined in Table 1; and an amino acid sequence of a secreted portion of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The isolated polypeptide produced by this method is also preferred.

Also preferred is a method of treatment of an individual in need of an increased level of a secreted protein activity, which method comprises administering to such an individual a pharmaceutical composition comprising an amount of an isolated polypeptide, polynucleotide, or antibody of the claimed invention effective to increase the level of said protein activity in said individual.

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

Examples

Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample

Each cDNA clone in a cited ATCC deposit is contained in a plasmid vector. Table 1 identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The table immediately below correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table 1 as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

Vector Used to Construct Library	Corresponding Deposited Plasmid
Lambda Zap	pBluescript (pBS)
Uni-Zap XR	pBluescript (pBS)
Zap Express	pBK
lafmid BA	plafmid BA

pSport1	pSport1
pCMVSport 2.0	pCMVSport 2.0
pCMVSport 3.0	pCMVSport 3.0
pCR®2.1	pCR®2.1

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3 primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the f1 origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the f1 ori generates sense strand DNA and in the other, antisense.

Vectors pSport1, pCMVSport 2.0 and pCMVSport 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993).) Vector lafmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain XL-1 Blue. Vector pCR®2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into E. coli strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., Nuc. Acids Res. 16:9677-9686 (1988) and Mead, D. et al., Bio/Technology 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 1, as well as the corresponding plasmid vector sequences designated above.

The deposited material in the sample assigned the ATCC Deposit Number cited in Table 1 for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone identified in Table 1. Typically, each ATCC deposit sample cited in Table 1 comprises a mixture of approximately equal amounts (by weight) of about 50 plasmid DNAs, each containing a different cDNA clone; but such a deposit sample may include plasmids for more or less than 50 cDNA clones, up to about 500 cDNA clones.

Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that clone in Table 1. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to SEQ ID NO:X.

Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with ^{32}P-γ-ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring, NY (1982).) The plasmid mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

Alternatively, two primers of 17-20 nucleotides derived from both ends of the SEQ ID NO:X (i.e., within the region of SEQ ID NO:X bounded by the 5' NT and the 3' NT of the clone defined in Table 1) are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25 μl of reaction

mixture with 0.5 ug of the above cDNA template. A convenient reaction mixture is 1.5-5 mM $MgCl_2$, 0.01% (w/v) gelatin, 20 μM each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., Nucleic Acids Res. 21(7):1683-1684 (1993).)

Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific

to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide

A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the cDNA sequence corresponding to SEQ ID NO:X., according to the method described in Example 1. (See also, Sambrook.)

Example 3: Tissue Distribution of Polypeptide

Tissue distribution of mRNA expression of polynucleotides of the present invention is determined using protocols for Northern blot analysis, described by, among others, Sambrook et al. For example, a cDNA probe produced by the method described in Example 1 is labeled with P^{32} using the rediprime™ DNA labeling system (Amersham Life Science), according to manufacturer's instructions. After labeling, the probe is purified using CHROMA SPIN-100™ column (Clontech Laboratories, Inc.), according to manufacturer's protocol number PT1200-1. The purified labeled probe is then used to examine various human tissues for mRNA expression.

Multiple Tissue Northern (MTN) blots containing various human tissues (H) or human immune system tissues (IM) (Clontech) are examined with the labeled probe using ExpressHyb™ hybridization solution (Clontech) according to manufacturer's protocol number PT1190-1. Following hybridization and washing, the blots are mounted and exposed to film at -70°C overnight, and the films developed according to standard procedures.

Example 4: Chromosomal Mapping of the Polynucleotides

An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions : 30 seconds, 95°C; 1 minute, 56°C; 1 minute, 70°C. This cycle is repeated 32 times followed by one 5 minute cycle at 70°C. Human, mouse, and

hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in the particular somatic cell hybrid.

Example 5: Bacterial Expression of a Polypeptide

A polynucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp^r), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan^r). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 ($O.D.^{600}$) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1

mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4°C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM immidazole. Immidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4°C or frozen at -80°C.

In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (lacIq). The

origin of replication (oriC) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

DNA can be inserted into the pHEa by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

Example 6: Purification of a Polypeptide from an Inclusion Body

The following alternative method can be used to purify a polypeptide expressed in *E coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10°C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

The cells are then lysed by passing the solution through a microfluidizer (Microfuidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is discarded and the polypeptide containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 μm membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant A_{280} monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5 μg of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

Example 7: Cloning and Expression of a Polypeptide in a Baculovirus Expression System

In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak Drosophila promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., Virology 170:31-39 (1989).

Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon and the naturally associated leader sequence identified in Table 1, is amplified using the PCR protocol described in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("Geneclean" BIO 101 Inc., La Jolla, Ca.).

The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

Five μg of a plasmid containing the polynucleotide is co-transfected with 1.0 μg of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One μg of BaculoGold™ virus DNA and 5 μg of the plasmid are mixed in a sterile well of a microtiter plate containing 50 μl of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10 μl Lipofectin plus 90 μl Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27° C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27° C for four days.

After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then

resuspended in a microcentrifuge tube containing 200 µl of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4° C.

To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 µCi of ^{35}S-methionine and 5 µCi ^{35}S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

Example 8: Expression of a Polypeptide in Mammalian Cells

The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLVI, HIVI and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109),

pCMVSport 2.0, and pCMVSport 3.0. Mammalian host cells that could be used include, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as dhfr, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., Biotechnology 9:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No.209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., Cell 41:521-530 (1985).) Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the vector does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five μg of the expression plasmid pC6 is cotransfected with 0.5 μg of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of metothrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 μM, 2 μM, 5 μM, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200 μM. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

Example 9: Protein Fusions

The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al., Nature 331:84-86 (1988).) Similarly, fusion to IgG-1, IgG-3, and albumin increases the halflife time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

If the naturally occurring signal sequence is used to produce the secreted protein, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

Human IgG Fc region:

GGGATCCGGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACCGTGC
CCAGCACCTGAATTCGAGGGTGCACCGTCAGTCTTCCTCTTCCCCCCAAAA
CCCAAGGACACCCTCATGATCTCCCGGACTCCTGAGGTCACATGCGTGGT
GGTGGACGTAAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGG
ACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTA
CAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACT
GGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCA
ACCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAAC
CACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAAGCGACATCGCCGT
GGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCT
CCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTG
GACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCA
TGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGG
GTAAATGAGTGCGACGGCCGCGACTCTAGAGGAT (SEQ ID NO:1)

Example 10: Production of an Antibody from a Polypeptide

The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) For example, cells expressing a polypeptide of the present invention is administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of the secreted protein is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

In the most preferred method, the antibodies of the present invention are monoclonal antibodies (or protein binding fragments thereof). Such monoclonal antibodies can be prepared using hybridoma technology. (Köhler et al., Nature 256:495 (1975); Köhler et al., Eur. J. Immunol. 6:511 (1976); Köhler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981).) In general, such procedures involve immunizing an animal (preferably a mouse) with polypeptide or, more preferably, with a secreted polypeptide-expressing cell. Such cells may be cultured in

any suitable tissue culture medium; however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 µg/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981).) The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide.

Alternatively, additional antibodies capable of binding to the polypeptide can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the protein-specific antibody can be blocked by the polypeptide. Such antibodies comprise anti-idiotypic antibodies to the protein-specific antibody and can be used to immunize an animal to induce formation of further protein-specific antibodies.

It will be appreciated that Fab and F(ab')2 and other fragments of the antibodies of the present invention may be used according to the methods disclosed herein. Such fragments are typically produced by proteolytic cleavage, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')2 fragments). Alternatively, secreted protein-binding fragments can be produced through the application of recombinant DNA technology or through synthetic chemistry.

For in vivo use of antibodies in humans, it may be preferable to use "humanized" chimeric monoclonal antibodies. Such antibodies can be produced

using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric antibodies are known in the art. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

Example 11: Production Of Secreted Protein For High-Throughput Screening Assays

The following protocol produces a supernatant containing a polypeptide to be tested. This supernatant can then be used in the Screening Assays described in Examples 13-20.

First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a working solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be poly-lysine coated in advance for up to two weeks.

Plate 293T cells (do not carry cells past P+20) at 2 x 10^5 cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing a polynucleotide insert, produced by the methods described in Examples 8 or 9, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45

minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on PBS. First, person A aspirates off the media from four 24-well plates of cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37°C for 6 hours.

While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with 1x penstrep, or CHO-5 media (116.6 mg/L of CaCl2 (anhyd); 0.00130 mg/L $CuSO_4$-$5H_2O$; 0.050 mg/L of $Fe(NO_3)_3$-$9H_2O$; 0.417 mg/L of $FeSO_4$-$7H_2O$; 311.80 mg/L of Kcl; 28.64 mg/L of $MgCl_2$; 48.84 mg/L of $MgSO_4$; 6995.50 mg/L of NaCl; 2400.0 mg/L of $NaHCO_3$; 62.50 mg/L of NaH_2PO_4-H_2O; 71.02 mg/L of Na_2HPO4; .4320 mg/L of $ZnSO_4$-$7H_2O$; .002 mg/L of Arachidonic Acid ; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitric Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L-Arginine-HCL; 7.50 mg/ml of L-Asparagine-H_2O; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-2HCL-H_2O; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L-Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L-Histidine-HCL-H_2O; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalainine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tryrosine-2Na-$2H_2O$; 99.65 mg/ml of L-Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319

mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; and 0.680 mg/L of Vitamin B_{12}; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; and 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml appropriate media to each well. Incubate at 37°C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 13-20.

It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the polypeptide directly (e.g., as a secreted protein) or by the polypeptide inducing expression of other proteins, which are then secreted into the supernatant. Thus, the invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

Example 12: Construction of GAS Reporter Construct

One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements alter the expression of the associated gene.

GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621-51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN-a, IFN-g, and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xxx-Trp-Ser (SEQ ID NO:2)).

Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway.

Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

Ligand	tyk2	JAKs Jak1	Jak2	Jak3	STATS	GAS(elements) or ISRE
IFN family						
IFN-a/B	+	+	-	-	1,2,3	ISRE
IFN-g		+	+	-	1	GAS (IRF1>Lys6>IFP)
Il-10	+	?	?	-	1,3	
gp130 family						
IL-6 (Pleiotrophic)	+	+	+	?	1,3	GAS (IRF1>Lys6>IFP)
Il-11(Pleiotrophic)	?	+	?	?	1,3	
OnM(Pleiotrophic)	?	+	+	?	1,3	
LIF(Pleiotrophic)	?	+	+	?	1,3	
CNTF(Pleiotrophic)	-/+	+	+	?	1,3	
G-CSF(Pleiotrophic)	?	+	?	?	1,3	
IL-12(Pleiotrophic)	+	-	+	+	1,3	
g-C family						
IL-2 (lymphocytes)	-	+	-	+	1,3,5	GAS
IL-4 (lymph/myeloid)	-	+	-	+	6	GAS (IRF1 = IFP >>Ly6)(IgH)
IL-7 (lymphocytes)	-	+	-	+	5	GAS
IL-9 (lymphocytes)	-	+	-	+	5	GAS
IL-13 (lymphocyte)	-	+	?	?	6	GAS
IL-15	?	+	?	+	5	GAS
gp140 family						
IL-3 (myeloid)	-	-	+	-	5	GAS (IRF1>IFP>>Ly6)
IL-5 (myeloid)	-	-	+	-	5	GAS
GM-CSF (myeloid)	-	-	+	-	5	GAS
Growth hormone family						
GH	?	-	+	-	5	
PRL	?	+/-	+	-	1,3,5	
EPO	?	-	+	-	5	GAS(B-CAS>IRF1=IFP>>Ly6)
Receptor Tyrosine Kinases						
EGF	?	+	+	-	1,3	GAS (IRF1)
PDGF	?	+	+	-	1,3	
CSF-1	?	+	+	-	1,3	GAS (not IRF1)

To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 13-14, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

5':GCGCCTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCC GAAATGATTTCCCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:3)

The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:4)

PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

5':CTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAA TGATTTCCCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCG CCCCTAACTCCGCCCATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCT CCGCCCCATGGCTGACTAATTTTTTTATTTATGCAGAGGCCGAGGCCGCC TCGGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCT AGGCTTTTGCAAAAAGCTT:3' (SEQ ID NO:5)

With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using SalI and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 13-14.

Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules containing NFK-B and EGR promoter sequences are described in Examples 15 and 16. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, Il-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

Example 13: High-Throughput Screening Assay for T-cell Activity.

The following protocol is used to assess T-cell activity by identifying factors, such as growth factors and cytokines, that may proliferate or differentiate T-cells. T-cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells (ATCC Accession No. TIB-152), although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

Jurkat T-cells are lymphoblastic CD4+ Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately 20,000 cells per well and transfectants resistant to 1 mg/ml genticin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

Specifically, the following protocol will yield sufficient cells for 75 wells containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1%Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies) with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

During the incubation period, count cell concentration, spin down the required number of cells (10^7 per transfection), and resuspend in OPTI-MEM to a final concentration of 10^7 cells/ml. Then add 1ml of 1 x 10^7 cells in OPTI-MEM to T25 flask and incubate at 37°C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Genticin, and 1% Pen-Strep. These cells are treated with supernatants containing a polypeptide as produced by the protocol described in Example 11.

On the day of treatment with the supernatant, the cells should be washed and resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100, 000 cells per well).

After all the plates have been seeded, 50 ul of the supernatants are transferred directly from the 96 well plate containing the supernatants into each well using a 12 channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.

The 96 well dishes containing Jurkat cells treated with supernatants are placed in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophene covers) and stored at -20°C until SEAP assays are performed according to Example 17. The plates containing the remaining treated cells are placed at 4°C and serve as a source of material for repeating the assay on a specific well if desired.

As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

The above protocol may be used in the generation of both transient, as well as, stable transfected cells, which would be apparent to those of skill in the art.

Example 14: High-Throughput Screening Assay Identifying Myeloid Activity

The following protocol is used to assess myeloid activity by identifying factors, such as growth factors and cytokines, that may proliferate or differentiate myeloid cells. Myeloid cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 12, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell Growth & Differentiation, 5:259-265) is used. First, harvest $2x10e^7$ U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing

10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.

Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM $Na_2HPO_4.7H_2O$, 1 mM $MgCl_2$, and 675 uM $CaCl_2$. Incubate at 37°C for 45 min.

Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37°C for 36 hr.

The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

These cells are tested by harvesting $1x10^8$ cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium, with a final density of $5x10^5$ cells/ml. Plate 200 ul cells per well in the 96-well plate (or $1x10^5$ cells/well).

Add 50 ul of the supernatant prepared by the protocol described in Example 11. Incubate at 37°C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant according to the protocol described in Example 17.

Example 15: High-Throughput Screening Assay Identifying Neuronal Activity.

When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed.

Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat phenochromocytoma cells) are known to proliferate and/or differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor).

The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells can be assessed.

The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG -3' (SEQ ID NO:6)

5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO:7)

Using the GAS:SEAP/Neo vector produced in Example 12, EGR1 amplified product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1 promoter.

To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and allowed to air dry for 2 hr.

PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine protocol described in Example 11. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS

(Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count the cell number and add more low serum medium to reach final cell density as $5x10^5$ cells/ml.

Add 200 ul of the cell suspension to each well of 96-well plate (equivalent to $1x10^5$ cells/well). Add 50 ul supernatant produced by Example 11, 37°C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR can be used, such as 50 ng/ul of Neuronal Growth Factor (NGF). Over fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay the supernatant according to Example 17.

Example 16: High-Throughput Screening Assay for T-cell Activity

NF-κB (Nuclear Factor κB) is a transcription factor activated by a wide variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF-κB regulates the expression of genes involved in immune cell activation, control of apoptosis (NF- κB appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

In non-stimulated conditions, NF- κB is retained in the cytoplasm with I-κB (Inhibitor κB). However, upon stimulation, I- κB is phosphorylated and degraded, causing NF- κB to shuttle to the nucleus, thereby activating transcription of target genes. Target genes activated by NF- κB include IL-2, IL-6, GM-CSF, ICAM-1 and class 1 MHC.

Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF-κB promoter element are used to screen the supernatants produced in Example 11. Activators or inhibitors of NF-kB would be useful in treating diseases. For example, inhibitors of NF-κB could be used to treat those

diseases related to the acute or chronic activation of NF-kB, such as rheumatoid arthritis.

To construct a vector containing the NF-κB promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF-κB binding site (GGGGACTTTCCC) (SEQ ID NO:8), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:
5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGAC TTTCCATCCTGCCATCTCAATTAG:3' (SEQ ID NO:9)

The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:
5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:4)

PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene) Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACTTTCC ATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCC ATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGA CTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTA TTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAA GCTT:3' (SEQ ID NO:10)

Next, replace the SV40 minimal promoter element present in the pSEAP2-promoter plasmid (Clontech) with this NF-κB/SV40 fragment using XhoI and HindIII. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

In order to generate stable mammalian cell lines, the NF-κB/SV40/SEAP cassette is removed from the above NF-κB/SEAP vector using restriction enzymes SalI and NotI, and inserted into a vector containing neomycin resistance. Particularly,

the NF-κB/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the GFP gene, after restricting pGFP-1 with SalI and NotI.

Once NF-κB/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 13. Similarly, the method for assaying supernatants with these stable Jurkat T-cells is also described in Example 13. As a positive control, exogenous TNF alpha (0.1,1, 10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

Example 17: Assay for SEAP Activity

As a reporter molecule for the assays described in Examples 13-16, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 µl of 2.5x dilution buffer into Optiplates containing 35 µl of a supernatant. Seal the plates with a plastic sealer and incubate at 65°C for 30 min. Separate the Optiplates to avoid uneven heating.

Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 µl Assay Buffer and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the table below). Add 50 µl Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at each time and start the second set 10 minutes later.

Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

Reaction Buffer Formulation:

# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3
11	65	3.25
12	70	3.5
13	75	3.75
14	80	4
15	85	4.25

16	90	4.5
17	95	4.75
18	100	5
19	105	5.25
20	110	5.5
21	115	5.75
22	120	6
23	125	6.25
24	130	6.5
25	135	6.75
26	140	7
27	145	7.25
28	150	7.5
29	155	7.75
30	160	8
31	165	8.25
32	170	8.5
33	175	8.75
34	180	9
35	185	9.25
36	190	9.5
37	195	9.75
38	200	10
39	205	10.25
40	210	10.5
41	215	10.75
42	220	11
43	225	11.25
44	230	11.5
45	235	11.75
46	240	12
47	245	12.25
48	250	12.5
49	255	12.75
50	260	13

Example 18: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability

Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small

molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-4 (Molecular Probes, Inc.; catalog no. F-14202), used here.

For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO_2 incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

A stock solution of 1 mg/ml fluo-4 is made in 10% pluronic acid DMSO. To load the cells with fluo-4 , 50 ul of 12 ug/ml fluo-4 is added to each well. The plate is incubated at 37°C in a CO_2 incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to 2-5x10^6 cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-4 solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37°C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to 1x10^6 cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley CellWash with 200 ul, followed by an aspiration step to 100 ul final volume.

For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-4 . The supernatant is added to the well, and a change in fluorescence is detected.

To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm; and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event which has resulted in an increase in the intracellular Ca^{++} concentration.

Example 19: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity

The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

Because of the wide range of known factors capable of stimulating tyrosine kinase activity, the identification of novel human secreted proteins capable of activating tyrosine kinase signal transduction pathways are of interest. Therefore, the following protocol is designed to identify those novel human secreted proteins capable of activating the tyrosine kinase signal transduction pathways.

Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (St. Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford,MA), or calf serum, rinsed with PBS and stored at 4°C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford,MA) are used to cover the Loprodyne Silent Screen

Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium. Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example 11, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na3VO4, 2 mM Na4P2O7 and a cocktail of protease inhibitors (# 1836170) obtained from Boeheringer Mannheim (Indianapolis, IN) is added to each well and the plate is shaken on a rotating shaker for 5 minutes at 4°C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well, after detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 4°C at 16,000 x g.

Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described here.

Generally, the tyrosine kinase activity of a supernatant is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg_{2+} (5mM ATP/50mM $MgCl_2$), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM $MgCl_2$, 5 mM $MnCl_2$, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the

components gently and preincubate the reaction mix at 30°C for 2 min. Initial the reaction by adding 10ul of the control enzyme or the filtered supernatant.

The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mm EDTA and place the reactions on ice.

Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37°C for 20 min. This allows the streptavadin coated 96 well plate to associate with the biotinylated peptide. Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phospotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37°C for one hour. Wash the well as above.

Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.

Example 20: High-Throughput Screening Assay Identifying Phosphorylation Activity

As a potential alternative and/or compliment to the assay of protein tyrosine kinase activity described in Example 19, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as described below one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G

plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1
and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4°C until use.

A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants obtained in Example 11 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place
of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation.

Example 21: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide

RNA isolated from entire families or individual patients presenting with a phenotype of interest (such as a disease) is be isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO:X. Suggested PCR conditions consist of 35 cycles at 95°C for 30 seconds; 60-120 seconds at 52-58°C; and 60-120 seconds at 70°C, using buffer solutions described in Sidransky, D., et al., Science 252:706 (1991).

PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies). The intron-exon borders of selected exons is also determined and genomic PCR products analyzed to confirm the results. PCR products harboring suspected mutations is then cloned and sequenced to validate the results of the direct sequencing.

PCR products is cloned into T-tailed vectors as described in Holton, T.A. and Graham, M.W., Nucleic Acids Research, 19:1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

Genomic rearrangements are also observed as a method of determining alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2 are nick-translated with digoxigenindeoxy-uridine 5'-triphosphate (Boehringer Manheim), and FISH performed as described in Johnson, Cg. et al., Methods Cell Biol. 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson, Cv. et al., Genet. Anal. Tech. Appl., 8:75 (1991).) Image collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

Example 22: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample

A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 10. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbounded polypeptide.

Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbounded conjugate.

Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the polypeptide in the sample using the standard curve.

Example 23: Formulating a Polypeptide

The secreted polypeptide composition will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the secreted polypeptide alone), the site of delivery, the method of administration, the

scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of secreted polypeptide administered parenterally per dose will be in the range of about 1 μg/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the secreted polypeptide is typically administered at a dose rate of about 1 μg/kg/hour to about 50 μg/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Pharmaceutical compositions containing the secreted protein of the invention are administered orally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

The secreted polypeptide is also suitably administered by sustained-release systems. Suitable examples of sustained-release compositions include semi-permeable polymer matrices in the form of shaped articles, e.g., films, or mirocapsules. Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman, U. et al., Biopolymers 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (R. Langer et al., J. Biomed. Mater. Res. 15:167-277 (1981), and R. Langer, Chem. Tech. 12:98-105 (1982)), ethylene vinyl acetate (R. Langer et al.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988). Sustained-release compositions also include liposomally entrapped polypeptides. Liposomes containing the secreted polypeptide are prepared by methods known per se: DE 3,218,121; Epstein et al.,

Proc. Natl. Acad. Sci. USA 82:3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci. USA 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal secreted polypeptide therapy.

For parenteral administration, in one embodiment, the secreted polypeptide is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to polypeptides.

Generally, the formulations are prepared by contacting the polypeptide uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrins; chelating agents such as EDTA; sugar

alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The secreted polypeptide is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any polypeptide to be used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutic polypeptide compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Polypeptides ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous polypeptide solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized polypeptide using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the polypeptides of the present invention may be employed in conjunction with other therapeutic compounds.

Example 24: Method of Treating Decreased Levels of the Polypeptide

It will be appreciated that conditions caused by a decrease in the standard or normal expression level of a secreted protein in an individual can be treated by administering the polypeptide of the present invention, preferably in the secreted form. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an

individual a pharmaceutical composition comprising an amount of the polypeptide to increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the polypeptide for six consecutive days. Preferably, the polypeptide is in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 23.

Example 25: Method of Treating Increased Levels of the Polypeptide

Antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, preferably a secreted form, due to a variety of etiologies, such as cancer.

For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 23.

Example 26: Method of Treatment Using Gene Therapy

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37°C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

Example 27: Method of Treatment Using Gene Therapy - In Vivo

Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the present invention may be operatively linked to a promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata H. et al. (1997) Cardiovasc. Res. 35(3):470-479, Chao J et al. (1997) Pharmacol. Res. 35(6):517-522, Wolff J.A. (1997) Neuromuscul. Disord. 7(5):314-318, Schwartz B. et al. (1996) Gene Ther. 3(5):405-411, Tsurumi Y. et al. (1996) Circulation 94(12):3281-3290 (incorporated herein by reference).

The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in

the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an

aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be use to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.

Example 28: Transgenic Animals.

The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, *e.g.*, baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a

specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

Any technique known in the art may be used to introduce the transgene (i.e., polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver et al., Biotechnology (NY) 11:1263-1270 (1993); Wright et al., Biotechnology (NY) 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., Cell 56:313-321 (1989)); electroporation of cells or embryos (Lo, 1983, Mol Cell. Biol. 3:1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, e.g., Ulmer et al., Science 259:1745 (1993); introducing nucleic acid constructs into embryonic pleuripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (Lavitrano et al., Cell 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115:171-229 (1989), which is incorporated by reference herein in its entirety.

Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell et al., Nature 380:64-66 (1996); Wilmut et al., Nature 385:810-813 (1997)).

The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells, *i.e.,* mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, *e.g.,* head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci. USA 89:6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the

particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the

transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

Example 29: Knock-Out Animals.

Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (*E.g.*, see Smithies et al., Nature 317:230-234 (1985); Thomas & Capecchi, Cell 51:503-512 (1987); Thompson et al., Cell 5:313-321 (1989); each of which is incorporated by reference herein in its entirety). For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (*e.g.*, see Thomas & Capecchi 1987 and Thompson 1989, *supra*). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (e.g., knockouts) are administered to a patient *in vivo*. Such cells may be obtained from the patient (i.e.,

animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (e.g., lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, e.g., by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc. The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, e.g., in the circulation, or intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, e.g., genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and Mulligan & Wilson, U.S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 198, line N/A

B. **IDENTIFICATION OF DEPOSIT** Further deposits are identified on an additional sheet ☐

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
April 20, 1998	209782

C. **ADDITIONAL INDICATIONS** *(leave blank if not applicable)* This information is continued on an additional sheet ☐

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B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☐

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Address of depositary institution *(including postal code and country)*
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Manassas, Virginia 20110-2209
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August 28, 1997	209226

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B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☐

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10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
March 13, 1997	97958

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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

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A. The indications made below relate to the microorganism referred to in the description on page 201, line N/A

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☐

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
May 7, 1998	209852

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

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A. The indications made below relate to the microorganism referred to in the description on page 204, line N/A

B. **IDENTIFICATION OF DEPOSIT** Further deposits are identified on an additional sheet ☐

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
May 7, 1998	209853

C. **ADDITIONAL INDICATIONS** *(leave blank if not applicable)* This information is continued on an additional sheet ☐

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E. **SEPARATE FURNISHING OF INDICATIONS** *(leave blank if not applicable)*

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It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. Further, the hard copy of the sequence listing submitted herewith and the corresponding computer readable form are both incorporated herein by reference in their entireties.

What Is Claimed Is:

1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a polynucleotide fragment of SEQ ID NO:X or a polynucleotide fragment of the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(c) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y or a polypeptide domain encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(d) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y or a polypeptide epitope encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(e) a polynucleotide encoding a polypeptide of SEQ ID NO:Y or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X, having biological activity;

(f) a polynucleotide which is a variant of SEQ ID NO:X;

(g) a polynucleotide which is an allelic variant of SEQ ID NO:X;

(h) a polynucleotide which encodes a species homologue of the SEQ ID NO:Y;

(i) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide sequence of only A residues or of only T residues.

2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a secreted protein.

3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.

4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.

5. The isolated nucleic acid molecule of claim 2, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

6. The isolated nucleic acid molecule of claim 3, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

7. A recombinant vector comprising the isolated nucleic acid molecule of claim 1.

8. A method of making a recombinant host cell comprising the isolated nucleic acid molecule of claim 1.

9. A recombinant host cell produced by the method of claim 8.

10. The recombinant host cell of claim 9 comprising vector sequences.

11. An isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(b) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z, having biological activity;

(c) a polypeptide domain of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(d) a polypeptide epitope of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(e) a secreted form of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(f) a full length protein of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(g) a variant of SEQ ID NO:Y;

(h) an allelic variant of SEQ ID NO:Y; or

(i) a species homologue of the SEQ ID NO:Y.

12. The isolated polypeptide of claim 11, wherein the secreted form or the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.

13. An isolated antibody that binds specifically to the isolated polypeptide of claim 11.

14. A recombinant host cell that expresses the isolated polypeptide of claim 11.

15. A method of making an isolated polypeptide comprising:

(a) culturing the recombinant host cell of claim 14 under conditions such that said polypeptide is expressed; and

(b) recovering said polypeptide.

16. The polypeptide produced by claim 15.

17. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of the polypeptide of claim 11 or the polynucleotide of claim 1.

18. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or absence of a mutation in the polynucleotide of claim 1; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of said mutation.

19. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or amount of expression of the polypeptide of claim 11 in a biological sample; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.

20. A method for identifying a binding partner to the polypeptide of claim 11 comprising:

(a) contacting the polypeptide of claim 11 with a binding partner; and

(b) determining whether the binding partner effects an activity of the polypeptide.

21. The gene corresponding to the cDNA sequence of SEQ ID NO:Y.

22. A method of identifying an activity in a biological assay, wherein the method comprises:

(a) expressing SEQ ID NO:X in a cell;

(b) isolating the supernatant;

(c) detecting an activity in a biological assay; and

(d) identifying the protein in the supernatant having the activity.

23. The product produced by the method of claim 20.

<110> Human Genome Sciences, Inc. et al.

<120> 94 Human secreted proteins

<130> PZ029PCT

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cagttccgcc cattctccgc cccatggctg actaattttt tttatttatg cagaggccga 180
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<210> 11
<211> 899
<212> DNA
<213> Homo sapiens

<400> 11
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<211> 1140
<212> DNA
<213> Homo sapiens

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<210> 13
<211> 1445
<212> DNA
<213> Homo sapiens

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<210> 14
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<212> DNA
<213> Homo sapiens

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<223> n equals a,t,g, or c

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<222> (59)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (79)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (814)
<223> n equals a,t,g, or c

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<210> 15
<211> 1175
<212> DNA
<213> Homo sapiens

<400> 15
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cttgatccaa gccaccctca gtcccactgc agttctcatc ctcggcccaa aagtcatcaa 180
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<210> 16
<211> 2374
<212> DNA

<213> Homo sapiens

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<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (2344)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (2346)
<223> n equals a,t,g, or c

<400> 16

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gtattctttt ataccttatt gggtttgtwt ttttacttac catggtaaaa atccatttga     180
gtgagcattc ttgagtggtt ttgcattgtg tcttcacaca gttgtaccat aattraagct     240
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<210> 17
<211> 1595
<212> DNA
<213> Homo sapiens

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tgtttattca ttttctaatc tatgctaaaa gcttttatca taagtcttgg gaacagttgt 180
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<210> 18
<211> 1287
<212> DNA
<213> Homo sapiens

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<223> n equals a,t,g, or c

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<222> (1202)
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<223> n equals a,t,g, or c

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<222> (1282)
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<210> 19
<211> 1396
<212> DNA
<213> Homo sapiens

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<222> (668)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (739)
<223> n equals a,t,g, or c

<220>
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<222> (751)
<223> n equals a,t,g, or c

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<210> 20
<211> 1277
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (1207)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1272)
<223> n equals a,t,g, or c

<400> 20
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<210> 21
<211> 1781
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (1494)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1496)
<223> n equals a,t,g, or c

<400> 21
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aaaattgggg gggggcccg gtaacccatt tggcccttta g 1781

<210> 22
<211> 1491
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (1425)
<223> n equals a,t,g, or c

<220>

<221> SITE
<222> (1426)
<223> n equals a,t,g, or c

<400> 22
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tgcttgaacc tgggaggcag aggttgcagt gagccgagac cacgnngttg cactccagcc 1440
tgggcaacaa gagtgaaact ctgtctcaaa aaaaaaaaaa aaaaactcga g 1491

<210> 23
<211> 1839
<212> DNA
<213> Homo sapiens

<400> 23
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ttggggaaat acccaaggct tcctgggaga agatagagaa ataaagagac agaggggaaa 1800
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aactcgtag 1839

<210> 24
<211> 1384
<212> DNA
<213> Homo sapiens

<400> 24
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tatcatgttt ctttggcctc cagtctctgg tgtttgccta agctttatta gagacaggtc 180
atttctacct atgtgtcatt ttatctatgt cttgatctta tgtaattcaa ttgctcttta 240
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aaaa 1384

<210> 25
<211> 1681
<212> DNA
<213> Homo sapiens

<400> 25
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a 1681

<210> 26
<211> 1949
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (1130)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1948)
<223> n equals a,t,g, or c

<400> 26
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aaaaaaaaaa agggggggggg gctagttnt 1949

<210> 27
<211> 2286
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (2262)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (2264)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (2272)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (2278)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (2279)
<223> n equals a,t,g, or c

<400> 27
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cgacgtagct tttggctttt ttctgggcta catgcagtac agcatcgtgg actattgctg 180
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ccatgatctt gatgtgctgc taggctggag cacacactgg ccattactga acacagccat 420
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<210> 28
<211> 530
<212> DNA
<213> Homo sapiens

<400> 28
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<210> 29
<211> 1296
<212> DNA
<213> Homo sapiens

<400> 29
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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaa 1296

<210> 30
<211> 1979
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (968)
<223> n equals a,t,g, or c

<400> 30
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aattttatgt ttgatgacta tatatttggg catatatctt gttggattag aataaataaa 1920
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<210> 31
<211> 1274
<212> DNA
<213> Homo sapiens

<400> 31
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ctttaatctt gccatttaaa ttacagtaga aagacaaaat caagtaaaat aaagtgttag 1260
ataatagaaa gagt 1274

<210> 32
<211> 1531
<212> DNA
<213> Homo sapiens

<400> 32
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aatggcagca aactcttcag gacaagcatt gcactctcga gaccctctct taataaggac 180
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<210> 33
<211> 2090
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (967)
<223> n equals a,t,g, or c

<400> 33
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ctaatcctcc ttattcctta tatcccagat ctggaactgg gcaaactatt aaaatgcaaa 180
cagaaaactt gggtgttgtt tattatgtca acaaggactt caaaaatgaa tataaaggaa 240
tgttattaca aaaggtagaa aagagtgtgg aggaagatta tgtgactaat attcgaaata 300
actgctggaa agaaagacaa caaaaaacag atatgcagta tgcagcaaaa gtataccgtg 360
atgatcgact ccgaagaagg cagatgcctt gagcatggac aactgtaaag aattagagcg 420
gcttaccagt ctttataaag gaggatgaac tggaattttt atttatacct tttagcgtac 480
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ctcctttaaa tagtaactga aaactaaaat ggaatatttt agttaacgct tctacaagta 660
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<210> 34
<211> 1006
<212> DNA
<213> Homo sapiens

<400> 34
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<210> 35
<211> 1787
<212> DNA
<213> Homo sapiens

<400> 35
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acctcagtat attctgcagt acctgtttga tacgaaaacc ggtgaggtcc aaacattgtg 180
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<210> 36
<211> 1201
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (29)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (48)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (63)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1201)
<223> n equals a,t,g, or c

<400> 36
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ccgctatctt ttgggttcat tccaaatagt tttgtgccat tgaaaaactt gaccttcaaa 180
aaaatttgtt tttcagaata gaacacaata ggacagtgac tgcacagttg tgaaaaagga 240
agagaatcat taaagaaaaa gaaaaaagat tttaagaccg ttgaaatcaa ttatcaagaa 300
cgtcctaaaa cacctatggc tttgactttg ttattgatcc agattatttt ccttgcattg 360
gggaaaatat ctttcatatt tgtttgctgt aaagatggtt ttgcaagaat aagtcatgac 420
caagacaaac tgccaataca aaagcccact gatactaatt atataatgag aaaaaaatgt 480
atccaactag gacacatatc ttttgagtta tttggactga aagcttaaga aaacttggaa 540
aattctattt tgtgatctag tcaagccaca gttatcaaag gctacatttt cagtgtaaga 600
taaatggatg agtaaactca aatatgtatc acgtgtgctt tgtatcttaa gatgtgtttc 660
caagagcatc tgaaattttg tttgtacatg tatcttgatc atttataaag ccactgtgat 720
ctataaatca agaaaatcca ttgtcataac cattttaaa agtcaaaaat taagacatcc 780
ttaattaaaa agtttcaaat ctagacacta aatgtgtgtg aatgtacaaa gaaaacaaac 840
cattgcttat gctgttatat actagagaaa ttttgttttg cttgctgttt taacttgaca 900
gatgaaggac tttagttgaa cttcatattg taagaactgt taataaaagt tgtcaagtaa 960
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cttgttattt gtcatgcacc agcattggag ataataaaat ttcttgttct gtgtaaaaaa 1140
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1200
n 1201

<210> 37
<211> 1896
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (444)
<223> n equals a,t,g, or c

<400> 37
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tcatgttcat ggtgctggag gtggtggtga gccgggtgac ctcgtcgctg gcgatgctct 120
ccgactcctt ccacatgctg tcggacgtgc tggcgctggt ggtggcgctg gtggccgagc 180
gcttcgcccg gcggacccac gccacccaga agaacacgtt cggctggatc cgagccgagg 240
taatgggggc tctggtgaac gccatcttcc tgactggcct ctgtttcgcc atcctgctgg 300
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tcggcgtggc cgggctgctg gtcaacgtgc tggggctctg cctcttccac catcacagcg 420
gcttcagcca ggactccggc cacngccact cgcacggggg tcacggccac ggccacggcc 480
tccccaaggg gcctcgcgtt aagagcaccc gccccgggag cagcgacatc aacgtggccc 540
cgggcgagca gggtcccgac caggaggaga ccaacaccct ggtggccaat accagcaact 600
ccaacgggct gaaattggac cccgcagacc cagaaaaccc cagaagtggt gatacagtgg 660
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gggctggaca acttaacatg cgtggagttt ttctgcatgt ccttggagat gccttgggtt 780
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aataaaattg ttactggaat ttctctgcaa aaaaaa 1896

<210> 38
<211> 1152
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (1145)
<223> n equals a,t,g, or c

<400> 38
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gcagccctgt gtcatcagtt gggaacagtg ctcttttgtg tccccacggg ggcctcatgt 180
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aagtgggaga tgtaaaccct tcagaaacac agtatatttc tgagcccaaa ctctgtccag 360
aatgcagaga aggcttattg tgtcagcagc agagggacct gcgtgaatac actcaagcca 420
ccatctatgt ccataaagtt gtggataata aaaaggtgat gaaggattcg gctccggaac 480
tgaatgtgag tagttctgaa acagaggagg acaaggaaga agctaaacca gatggagaaa 540
aagatccaga ttttaatcaa agcmatggtg gaacaaagcg gcaaaagata tcccatcaaa 600
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actgtcccaa atgccttatg tcaaataaag cagattgcac tgatggaaaa aaaaaaaaaa 1140
aaaanactcg ag 1152

<210> 39
<211> 1017
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (822)

<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (994)
<223> n equals a,t,g, or c

<400> 39
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agccctcgtg ggatggatca caggtgctgc tgtggcggtc ctgctgctgc tgctgctgct 180
ggccacctgc cttttccacg gacggcagga ctgtgacgtg gagaggaacc gtacagctgc 240
agggggaaac cgagtccgcc gggcccagcc ttggcccttc cggcggcggg gccacctggg 300
aatctttcac catcaccgtc atcctggcca cgtatctcat gtgccgaatg tgggcctcca 360
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ccaccatccc cgccacgctc gctgargctg ctgtcgccgg tgcctgtgga cagcagctgc 480
ccctgccctc ccatctgttc ccaggacaag tggaccccat gtttccatgt ggaaggatgc 540
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tcaattcatc ggtgccttag tccaagaaaa taaaaaccac taagaaaaaa aaaaaaaaaa 960
aatgaccctc gagggggggc ccggtaccca attngcccta tgaagaggcg aacagga 1017

<210> 40
<211> 1777
<212> DNA
<213> Homo sapiens

<400> 40
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ggagccggct gctggcatgg gtgctgtggc tgcaggcctg gcaggtggca gccccatgcc 120
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cccatcatgt ttacagggtt cggcggcagc gtttgttcca gaacgccgcc tcccacccag 1680
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aataaagagc tcttttctta aaaaaaaaaa aaaaaaa 1777

<210> 41
<211> 1003
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (990)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1002)
<223> n equals a,t,g, or c

<400> 41
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accaaatggg cacaaaagaa ccaggatacc aaaagttaag ctcatacagc tgcaaaccat 180
atcacttctt ggtaacaatg cagacctcat aaacctaaag aagagaaaga aaagaaaact 240
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aattcctcaa gggacagaaa aaaaattgga gactgttgaa atgcagattt gaagtaattt 660
ttttaaaata ttattttggg ttctgcgaca ttgtgaaaaa ttaaagttgt tgtgcaatac 720
ttaattcaga catgtaccac aagttaatgg tagactaaca ctgggggtg gggtctaggc 780
atcatgcttt tgtcagcata ctcttgagct tttaagtcta ctatgtctga actgtggttt 840
cttgtttatc ctttttttcct tagttggact gtaatgtatg gtctgtcaac ctgtgaatct 900
ttaaagtatg attcaggtat tgttgtattc tttactgtgt aataaaaaag ttgaaaaaaa 960
aaaaaaaaaa acccaagggg gggcccggtn cctttccccc tnt 1003

<210> 42
<211> 1201
<212> DNA
<213> Homo sapiens

<400> 42
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aatgaaaaaa cacaccaaat gtcagtggct taaaatgacc atccttttttc tcacagttat 120
gaagattggc tatggcacct ctgcttcctg ctataggcct gaggttctag ggcttcttat 180
gcctcatcct ctttaagcca aagggatagc cagagcatct tgatggcaga agtgcaataa 240
gatgagcccc actgctcggg tacattttca gcccctggtt gtgtcatgtc tactgatatc 300
tcattggtca aaggaagtca gagggccaag atgaagaggc agggaaatat gcactgccca 360
cagtgaagcc atgacaagag tgaggatgca ggaaggcatg aagaattggg gccaacagtt 420
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c 1201

<210> 43
<211> 1176
<212> DNA
<213> Homo sapiens

<400> 43
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atggcaaacc tagaatccta gactgccgct ccccagagga ggttctttaa gactgctcag 120
ctctcctgcc aatagcaaca atgcaaaagc ttacccttc tcccgtttcc ccagccccat 180
cttcatgtcc tgtggatgtt gcttcatcca catttataat ttactcctgt ctctctgcta 240
tggtttgggt gttgaaagag tgaagttctt tacctttagt attttaaaaa aagaaacaat 300
gttgctcaat tatttattct aaatatgttg ttgggctttg ctttatttac cctgtttgca 360
tgtcttgttg atgtcttttc agtccttatg gcccatcgac ttccttatcc atgacccaga 420
gaggccccag tgatattttg acttttcaaa tgtggtgaat aagtgagagt tgtttgttga 480
gttaactgtg attttaaata ttctgattgt tgtgaggcac ttttctaggt gtttgatttc 540
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aaaaaaaaaa aaaaaaaaaa ctcgaggggg ggcccg 1176

<210> 44
<211> 569
<212> DNA
<213> Homo sapiens

<400> 44
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cgttcctgac aagtcaggtg ttcagattgc agtccctggc caacgtcagg attcttacag 180
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caaacccccc tccaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 480
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 540
aaaaaaaaaa aaaaaaaaag gggggggcc 569

<210> 45
<211> 986
<212> DNA
<213> Homo sapiens

<400> 45
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aaaaaaaaaa aaaaaagggc ggccgc 986

<210> 46
<211> 1540
<212> DNA
<213> Homo sapiens

<400> 46
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tcctcatgta cagagcaatt gacagctttc cccgttggcg ttcctacttc tatttcatca 120
ctctcatttt cttcctcgcc tggcttgtga agaacgtgtt tattgctgtt atcattgaaa 180
catttgcaga aatcagagta cagtttcaac aaatgtgggg atcgagaagc agcactacct 240
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<210> 47
<211> 792
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (759)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (760)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (774)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (779)
<223> n equals a,t,g, or c

<400> 47
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gctctgcagc tggttgtctg gtactgctgg cctttgcttt ctatttagca tgttccttct 180
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aggggaattc cc 792

<210> 48
<211> 1497
<212> DNA
<213> Homo sapiens

<400> 48
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cgtctgacgt tttttccttt cggttacatg tccgtatctc ctctttcccc tttttcccct 240
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<210> 49
<211> 1340
<212> DNA
<213> Homo sapiens

<400> 49
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aaaaaaaaaa aaaaaaaaaa 1340

<210> 50
<211> 1539
<212> DNA
<213> Homo sapiens

<400> 50
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cagcccragg aagggaccca ataacctttc aaaacscaaa ctgctkcctg cggtgagggc 180
ccagggtcct ccacggagag gacaggcatc ttcctttccc accaggaagg agtcagcccg 240
gagcctctgc tatgtgcaag gcggtgtgca agcaccggct gcrgctyttt gctgtctctt 300
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catagctctc tccctagagt gagtcgaatg aggttcata 1539

<210> 51
<211> 1423
<212> DNA
<213> Homo sapiens

<400> 51
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cctaccatag gctactatac tgataatata aatgaaaccg aacatttttt gctactaact 480
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ctaaatttat gtaaaattgt ataaaataga attagaagtc actaagttct ttctgtgtag 1380
aagtaataaa tttattgtaa cacaaaaaaa aaaaaaaaaa aaa 1423

<210> 52
<211> 1364
<212> DNA
<213> Homo sapiens

<400> 52
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<210> 53
<211> 2288
<212> DNA
<213> Homo sapiens

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<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1279)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1798)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (2280)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (2285)
<223> n equals a,t,g, or c

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<210> 54
<211> 1512
<212> DNA
<213> Homo sapiens

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<222> (2)
<223> n equals a,t,g, or c

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<222> (8)
<223> n equals a,t,g, or c

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<223> n equals a,t,g, or c

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<223> n equals a,t,g, or c

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<222> (29)
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<222> (528)
<223> n equals a,t,g, or c

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<221> SITE

<222> (600)
<223> n equals a,t,g, or c

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<210> 55
<211> 1357
<212> DNA
<213> Homo sapiens

<400> 55
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gaaagtttac atttttatg ctttgtgttg gtgtgtaatt tttgtactct tggtggctag 1200
tttttgtcaa atctttttg gaatattgct taaatgtttt gattttatga tagtgaagct 1260
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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaa 1357

<210> 56
<211> 1989
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (31)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (161)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (162)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1702)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1943)
<223> n equals a,t,g, or c

<400> 56
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aggacctcaa agtaatgttt atccagaaac tgctatcatt accagggatt cattcgtgta 120
tttaacaaca tggggcatac attttggcca aatttgaaaa nntcttaaca tacaccccaa 180
aatccctgcc ccaaatttaa gaactagggt ggacacagtg cgtttttcca tgtcgcatct 240
tctgtgatgg ggctacgata cgtgggagca gagaatgggg aggttggagc gcatgccaga 300
tgaggatcta tcagcaatgg gacgggkcct ccactttagc atctcyaccc tgctcctytc 360
agaggaccgc ctttcattgc attcagctgt gatggtagca cgaacacagg tgcaccgagg 420
acgaggagag caggagcctt gtgctctctc tgcatctgag gcaggacagc acagggtayg 480
gagcagtctg cagagaggcc agctcatcag ggaagcactt gtcttccacc ttgggctttg 540
actgagcact gggcaattgg mcyctgggga tcaaygaaat aatcctaarc agagttactc 600
tatgtcacac tatggaatgt tccaagtasr tggccgtgtt ttcaaaagat rtattttctc 660
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cactcraatg tttgctgact cctactctgt gtgactgggg tgtacagcta tggactgatg 780
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gccgaagaaa aaaggctcgg gagtccagcc ccaagggags tggaacagcc ycacacacag 1320
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cataaggcag cagtctctgt gctgamaccc ttctccaagg gcgcgccttc tacctccagc 1440
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cattttatag aaaccactaa tataaaagac acaactgcaa gaaatgcctt ggaagaaaat 1860
gtttttatgg aaaacactaa catgccagaa gtcaccatct ctgaaaacac aaactacaat 1920
catcctcctg aggcagattc cgntgggact gcattcaact tagggccaac tgttaaacaa 1980
actgagaca 1989

<210> 57
<211> 2543
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (2538)
<223> n equals a,t,g, or c

<400> 57
ctccgttgga aacttgggct gagtaccgcg gcgggcgcga gcraggcgcc ctagacatct 60
tctccctccc ttgcctcaga tttattgcta aacatgggtg cattttgga taaacccaaa 120
actgaaaaac ataatgctca tggtgctggg aatggtttac gttatggcct gagcagcatg 180
caaggatgga gagtggaaat ggaagatgca cacacagctg ttgtaggtat tcctcacggc 240
ttggaagact ggtcattttt tgcagtttat gatggtcatg ctggatcccg agtggcaaat 300
tactgctcaa cacatttatt agaacacatc actactaacg aagactttag ggcagctgga 360
aaatcaggat ctgctcttga gctttcagtg gaaaatgtta agaatggtat cagaactgga 420
tttttgaaaa ttgatgaata catgcgtaac ttttcagacc tcagaaacgg gatggacagg 480
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ggtgattcac gtgctgttct gtataggaat ggacaagtct gcttttctac ccaggatcac 600
aaaccttgca atccaaggga aaaggagcga atccaaaatg caggaggcag cgtgatgata 660
caacgtgtta atggttcatt agcagtatct cgtgctctgg gggactatga ttacaagtgt 720
gttgatggca agggcccaac agaacaactt gtttctccag agcctgaggt ttatgraatt 780
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tgtatttggg aataatatta taaacccttm caaattttat gcatgtatct actgcatcct 1920
tcaactctca ctagaaaatc ttttgaaacc aaatggatta atttatggct atttataatt 1980
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gattgtcaca taaggtactt gaagatttat tagtttaatt ctatttttac agtaaccttg 2340
aattcttctg agttttgcat gtattaaatt caattaatgc tgaacatgaa gagtaaagta 2400
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atgtagttgc ccttgtgnag gtt 2543

<210> 58
<211> 777
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (766)
<223> n equals a,t,g, or c

<400> 58
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cccactcccg ksggatctat cttgggatcc catggctttc tttactgggc tctggggccc 120
cttcacctgt gtaagcagag tgctgagcca tcactgtttc agcaccactg ggagtctgag 180
tgcgattcag aagatgacgc gggtacgagt ggtggacaac agtgccctgg ggaacagccc 240
ataccatcgg gctcctcgct gcatccatgt ctataagaag aatggagtgg gcaaggtggg 300
cgaccagata ctactggcca tcaagggaca gaagaaaaag gcgctcattg tggggcactg 360
catgcctggc ccccgaatga cccccagatt ygactccaac aacgtggtcc tcattgagga 420
caacgggaac cctgtgggga cacgaattaa gacacccatc cccaccagcc tgcgcaagcg 480
ggaaggcgag tattccaagg tgctggccat tgctcagaac tttgtgtgag ttgagcccag 540
gcctctggtt gcaggactcg tgaatggagc agttctgaga accacccttt tgctaaggga 600
gcttgggagc cacatggctg ctcccttcac actgggtaac agtgtagtat cctgtgagag 660
aataaatgta ttcatttatg tgtttttcca gagctttctg ggatgtggga aaataaatta 720
cactgaagca gttgaaaggt gaaaaaaaaa aaaaaaaaaa aaaaanaaaa actcgag 777

<210> 59
<211> 879
<212> DNA
<213> Homo sapiens

<400> 59
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cctcagctgc agtggaggca cctcgggctc tggggcaacc aagtgtgaca ggtggctgtg 120
cacgggcaga ggtcctgtgg aagatttcat gtgacgggca gaagaggagg aggaggcagg 180
ggaggaagca catccatgaa cagggctgtc tgggggcagc ctgggtggtc gtgaaatagg 240
actcagtggc cttgagtcct catttaggcc ctgatgttct ttagcctgcc tggcctttgg 300
caaatcgcca gcttcacgca caacctcatt tttcaccttt gggtgtgggg gtcagagtcg 360
ggagagcacc tgcaaagcca caatgatcca gacacacggc aaggtgggca cattcccatc 420
aggctcctcg gggagagcag cgcttctgtg cccgggagca gcgaaggtca cacaggagga 480
cccgcacctc ctcgtgtcgg tggctccgct ggtataatca ggactcacgt ggtgttcctc 540
gtgtcgtggc ccttattgca gagggagcag cacaggcttt cctggaagct ccctcggtc 600
atgtggggtg actccagaga rccccacctt gcgagactgg accagtccaa gtggcctkga 660
gccacarcgg cctkgcagta cctkgggagg gggtgatgac aggtgcacac ggaggcccat 720
gtggtctgtc tggagaatgc cggagatgtg aaatatgtaa tcctgagtgt ggcttctaga 780
aggaaggttc gcaaagctga atatccactc gtgctgttcc cttctcacag gagattcctg 840
tcaacgtccg attctgcctc gaaggcagga ggagtaagg 879

<210> 60
<211> 1161

<212> DNA
<213> Homo sapiens

<400> 60
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ccgggccctg gagatggtcc ccggcgccgc gggctggtgt tgtctcgtgc tctggctccc 180
cgcgtgcgtc gcggcccacg gcttccgtat ccatgattat ttgtactttc aagtgctgag 240
tcctggggac attcgataca tcttcacagc cacacctgcc aaggactttg gtggtatctt 300
tcacacaagg tatgagcaga ttcaccttgt ccccgctgaa cctccagagg cctgcgggga 360
actcagcaac ggtttcttca tccaggacca gattgctctg gtggagaggg ggggctgctc 420
cttcctctcc aagactcggg tggtccagga gcacggcggg cgggcggtga tcatctctga 480
caacgcattg acaatgacag cttctacgtg gagatgatcc aggacagtac ccagcgcaca 540
gctgacatcc ccgccctctt cctgctcggc cgagacggct acatgatccg ccgctctctg 600
gaacagcatg ggctgccatg ggccatcatt tccatcccag tcaatgtcac cagcatcccc 660
acctttgagc tgctgcaacc gccctggacc ttctggtaga agagtttgtc ccacattcca 720
gccataagtg actctgagct gggaagggga aacccaggaa ttttgctact tggaatttgg 780
agatagcatc tggggacaag tggagccagg tagaggaaaa gggtttgggc gttgctaggc 840
tgaaagggaa gccacaccac tggccttccc ttccccaggg cccccaaggg tgtctcatgc 900
tacaagaaga ggcaagagac aggccccagg gcttctggct agaacccgaa acaaaaggag 960
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ccctacccag ggtctctgca cagtgacctt cacagcagtt gttggagtgg tttaaagagc 1080
tggtgtttgg ggactcaata aaccctcact gacttttag caataaagct tctcatcagg 1140
gttaaaaaaa aaaaaaaaaa a 1161

<210> 61
<211> 687
<212> DNA
<213> Homo sapiens

<400> 61
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tttactgcca ggtagcaggc tttattggga agggacaaag cctcaggagc tgggtgcccc 120
agaggctgct gggtcttgag ccacagctgc agccaatgca gcagtcgcgc ctccttcttc 180
cgtttctgtt tttcctcctt gagggttgcg ctccttcttc tctaggtcct ggagcagctc 240
ctggaagcgg gcactccttg ggtccacctg gtagcccagg agctcctggg cctcagcctg 300
cagtcgggcc ctcctctcct tgtcagcctg ggccttctcc cagttctccc gctgctgctg 360
ctgccagttc acaatcatct gtggcatctt ggccatgcac tctgcgatgt gctgctccct 420
ctcccgacgc ttctgctctt cggccagctg cttcacccgc agcgactcct gcatggtcgc 480
caggctcggg taccattcgc gttcttcggc ctccagctcc cgcagctgct ccggcgacgg 540
ccataacgaa ccggggacca ccccggaggc ggcgccgtaa cgcgcgaact gcttagcgcg 600
tagcgcggtc ccagctgcca ccgcggggtc aggaggtcct cggggtctgg ccaccggggt 660
cccggtgcgg cgcgggggcg gccgctc 687

<210> 62
<211> 518
<212> DNA
<213> Homo sapiens

<400> 62
acgcgtccga gatacattcc atgaatacct agtttattga gagtttttag catgaaggac 60
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ttggttctgt ttatgtgatg gactatgttt attgatttgc atatgttgaa ccagccttgc 180
atctcaggga tgaagccaac tcgatcgttg tggataagct ttttgatgtg ctgctggatt 240
tggtttgcca atattttatt gaggattttt gcatcagtgt tcttcaggga tattggtcta 300
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ataaatgagt tagggaggat tccctctttc tattgatcag aatagtttca gaaggaatgg 420
taccagctct tctttgtacc tctggtagaa tttgggtgtg aatctatctt gtcctggaat 480
atttttgggg ttggaactca aaaaaaaaaa aaaaaaaa 518

<210> 63
<211> 911
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (911)
<223> n equals a,t,g, or c

<400> 63
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ccctggcgat gtgctccagc ccaagcagcc tccgtaggct ttagatcctg tggttgccag 120
atccagtcct ttctaatacc ctgagtcaac acattactcc tgcaggtctt aggctacaat 180
gcaggtccct tgagggccac caacatggag gtaggcagtt tctaggactg tccccagtac 240
atctcaccac ccacagccct ttttttgcct tgattcgagc ctcaccctgg ccttttggct 300
tcccctgcct gagagagacc tgaggagggg acagagccca gcccctctcc tgtggctgag 360
caggcctctg tgtccatgac acctgtcttc cgggcctggg ggctgtgggt gtatgtcctc 420
cctactggct tccccggccc ctgctgcatg atgctcttgg aactcttccc caaggagtca 480
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tccatcaggt acagcttgca tttcaggatg tgtggaaagc tcgggtgagg gctgccctgg 600
ttcatcatag ctccaccttc ctcggaagga gtgggctgtt ggagaccccc catccatggc 660
acactagctc agcactgcat ttcccgagat gattcccaag acagctggtg cctcctggct 720
ttcctgtgcc aggccaaggg gcaccacaga ggaccctgga tcctttgcct cttcttggtt 780
gaaggatctc tatgtatgtg tgtatataaa tatagttttt tatctatata tataaaaaaa 840
aaaaaaaaaa aaaaaaaact cgaggggggg cccggtaccc aattcgccat atggtgatgg 900
caaatgggaa n 911

<210> 64
<211> 963
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (2)
<223> n equals a,t,g, or c

<400> 64
tncagaggcc ctgcggagtt gttcagaacc ccaactctct ctggctggct acccccctgaa 60
ctactgggtc tctggaccca ttgtgcccag ccacccccaa aagccctcag gcgagagctg 120
cctgaggagg caccgctgag gaggaaagga gaaagattga agttccaagt gagattgaga 180
gatctcccta gaggcagctg aagaggagaa gtcccgcatc agcctcatcc caccagaaga 240
acggtggtaa gcggccaggc tccgtggrag ccagggccca magcccttgg ccagktkgtg 300
gaaacagctg ctgggatggg tatgcccctt gtcactgtca cagctgccac cttccctact 360
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acccgggctg aagcctctgc taatggttct tgatccctat agggcagtgg cactggagyt 600
gcaggctaac agggagcccg acttcagcag cctggtgtca mctctcagcc cccgcaggat 660
ggctgcccgg gtcttctamc tgctcctggg tgartgtatg catgtgtgtg tgtgtatgtk 720
gggcagggac acagagacca gaggcccgta cagggactcc cccgacctgc cctctcctcg 780
cctcttgacc agtgctctca gcgcaacaga ttcttcacgt gaaacaagaa aagccatatg 840
gtcgcctcct gatccagccg gggcccagat tccactgagg ttagagtcca tttacaaagc 900
tgccaggaaa ccggccactt ctagtaaacc acgtcgtgcc tcactgaaaa aaaaaaaaaa 960
agg 963

<210> 65

<211> 1001
<212> DNA
<213> Homo sapiens

<400> 65
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aattttctaa ttgagaatgt tggcgctgtc cgaacctgga gacagagtat cagcgccttt 180
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aaccagggac cctctgcccc tagaataagr acatactaga agtcccttct gctaggacaa 420
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tcacccaggt cccccaggtc ctcaacacca ctgagaggct cctgctgagc ttcaactata 600
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ggagccagta taccccccttg actattgaca aggaggcctt cagaaacctg cccaacctta 720
gaatcttgga cctgggaagt agtaagatat acttcttgca tccagatgct tttcagggac 780
tgttccatct gtttgaactt agactgtatt tctgtggtct ctctgatgct gtattgaaag 840
atggttattt cagaaattta aaggctttaa ctcgcttgga tctatccaaa aatcagattc 900
gtagccttta ccttcatcct tcatttggga agttgaattc cttaaagtcc atagattttt 960
cctccaacca aatattcctt gtatgtgaac atgagctcga g 1001

<210> 66
<211> 1558
<212> DNA
<213> Homo sapiens

<400> 66
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<210> 67
<211> 1322
<212> DNA

<213> Homo sapiens

<220>
<221> SITE
<222> (11)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (690)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (719)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (720)
<223> n equals a,t,g, or c

<400> 67
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tatgccaaca tttaaaaagg ccaaaaccag aggcctagaa aatgtatctg gaagttgcag 180
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ag 1322

<210> 68
<211> 865
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (445)
<223> n equals a,t,g, or c

<400> 68
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cccccgaaag acccacttac tgtacatcct caggccctct cggcagctgt aggggtgggg 780
accggggagc acctgcctgt agcccccatc agaccctgcc ccaagcacca tatggaaata 840
aagttctttc ttacatctaa aaaaa 865

<210> 69
<211> 1150
<212> DNA
<213> Homo sapiens

<400> 69
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atatatcact caaaaaaccc agaagttgat gacagcagtg ctcagaaggg ctggtggttt 180
ctgagctggt ttaacaatgg gatccacaat tatcaacaag gggaagaaga catagacaaa 240
gaaaaaggaa gagaggagac caaaggaagg aaaatgacac aacagagctt cggctatggg 300
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gaccacctgt tgggactgcg agattctcaa ggggaaggac tgggtctcat ttctcccatc 480
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ccttctttcc taccctccac tttatctgca aaatgggaat gatgataaca cccacttcat 660
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tgtaagctac taaaaacaac aacaaaaaag gctcatcatt tctcagtctg aattgacaaa 1080
aatgccaatg caaataaaaa tgattacttt ttattttaaa aaaaaaaaaa aaaaaaaaaa 1140
aaaaaaaaaa 1150

<210> 70
<211> 1398
<212> DNA
<213> Homo sapiens

<400> 70
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tgagcctgac tccccaaccc ccacaaccct tttatatata tatggcatat tacagtgaga 180
atttcttttt aaagttttag gtctttgtct ttttcttgat aaaattatag ttataatagt 240
tgtcataagt taatcaatcg tatgttttaa gtgcccttag tgcaaaattt gatgcccctg 300
gatactgttg atttattaat atgaaatata cctttgttaa tttttaattt tatggatagg 360
tgtatatgtt tatggggtgt gagatacaac ttactctatt tacgttactt accgcagaac 420
cacatatttc ttccaaatgt ccatgcccta tcttagttac aaaaacacaa tcatttgcca 480
agtgaattat cggtgattat tagaaatcat ttatactgtg gttctgtgtg catttaaact 540
ataatatact tagaaattat tcttgctttg gtaaaatact ttccttctta ttcaagagga 600
ttttttgggt catgctgtct tgttatatac tcttttaagt ttattatgat tgtgtgtgta 660

tatgtttgtt ttttcttttt ccttctgtct gaattctgtt gcactgagca atgttgtaat 720
atttttattt taaatataag taatatttaa aattactgga aatatgtaac catcagatta 780
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aaaaaaaaaa aactcgta 1398

<210> 71
<211> 1557
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (1541)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1549)
<223> n equals a,t,g, or c

<400> 71
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acactccctg aatgctgtgc tgttggtttc cctggaggat tcttgctgca ggccaggtcc 120
cgtattctcc acactcacca caagtggctg ggtgtgactt gacacggtgt gaaagtggag 180
gggcgcgagc actcagtatc cagcgagcag cattggtggt cctagaaaat tactacaaag 240
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<210> 72
<211> 1163

<212> DNA
<213> Homo sapiens

<400> 72
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aagcgaaaaa aaaaaaaaaa aaa 1163

<210> 73
<211> 1486
<212> DNA
<213> Homo sapiens

<400> 73
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gcccctgagc gatgatgcga acgtgcgtct tactctccgc ggtgctctgg tgcctcacag 120
gagtccaatg cccgcgtttt accttattca ataagaaggg cttcatttat ggcaagacag 180
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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaa 1486

<210> 74
<211> 1553

<212> DNA
<213> Homo sapiens

<400> 74
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gggggttagg gaagatggtc gcttttccgg ttccgggtag gggggtctcc agaaagcccc 180
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<210> 75
<211> 1650
<212> DNA
<213> Homo sapiens

<400> 75
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<210> 76
<211> 2150
<212> DNA
<213> Homo sapiens

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<222> (874)
<223> n equals a,t,g, or c

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<222> (1198)
<223> n equals a,t,g, or c

<220>
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<222> (1201)
<223> n equals a,t,g, or c

<220>
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<223> n equals a,t,g, or c

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<210> 77
<211> 1592
<212> DNA
<213> Homo sapiens

<400> 77
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catgtatata catgtatata cacacatata catatatata catatatata cacacacata 600
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<210> 78
<211> 1579
<212> DNA
<213> Homo sapiens

<220>
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<222> (1529)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1556)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1569)
<223> n equals a,t,g, or c

<400> 78
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<210> 79
<211> 1396
<212> DNA
<213> Homo sapiens

<400> 79
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aaaaaaaaaa aaaaaa 1396

<210> 80
<211> 1230
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (1223)
<223> n equals a,t,g, or c

<400> 80
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<210> 81
<211> 1139
<212> DNA
<213> Homo sapiens

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<210> 82
<211> 1409
<212> DNA
<213> Homo sapiens

<400> 82
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<210> 83
<211> 714
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (704)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (709)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (714)
<223> n equals a,t,g, or c

<400> 83

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<210> 84
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<212> DNA
<213> Homo sapiens

<400> 84
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<210> 85
<211> 1931
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (1904)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1914)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1921)
<223> n equals a,t,g, or c

<400> 85
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nttacgttac g 1931

<210> 86
<211> 1092
<212> DNA
<213> Homo sapiens

<400> 86
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ccactacctg cccgcactca ccttccaaat ccttctgctc cctgtggtcc tgcagcacat 180
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ccactgagac gtggctgagt gaaatcttcc tcgtcagtgg tcaaggtgtg tcatccatac 1020
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aaaaaaaaaa aa 1092

<210> 87
<211> 578
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (576)
<223> n equals a,t,g, or c

<400> 87
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tgsggcctgg gacactgttg tccctcctct ccctaggaag tgccagtgca gcggcagtgc 240
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gactcctacc agagcatccg tccagctcag ccatccagcc tgtctctact gggccccact 480
tctctggatc agagaccctg cctctgtttg accccgcact gactgaataa agctcctctg 540
gccgtttaaa aaaaaaaaaa aaaaaaaaaa gggggncc 578

<210> 88
<211> 699
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (661)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (694)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (696)
<223> n equals a,t,g, or c

<400> 88
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ccacagacat gagtgcaggt aagtggctcc tgctggtgat cttcagggat ttgggatgcg 120
gagtttccag gacgtctccg cacttgagga gtggagagga gggaaggatc tggagcctac 180
tcacagcctg ctcctgctgt tgcctcttcg tgatcttcta gtggttcttg gcgaaatcag 240
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aggttgctgg ggcaagtgga ggcaggatag aagtgaaggg ctgtgggatg gagaacctca 660
naagactcca tctggggtcc gggaaaggac agananggt 699

<210> 89

<211> 1126
<212> DNA
<213> Homo sapiens

<400> 89
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agtgggggca gattctgctg ctggggaagg aaacaggagc ctggttcaca gyttagtgat 180
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<210> 90
<211> 1037
<212> DNA
<213> Homo sapiens

<400> 90
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cctccatcta tctccacgac cagaacccgg atgccgccct gcgtgcgctg caccaggggg 480
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ggtgcccccc tccaccctag gatgtgactc cgggccatgt ccagggcact ggtcacagaa 960
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aagctgggca tttcatg 1037

<210> 91
<211> 1316
<212> DNA
<213> Homo sapiens

<400> 91
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ccggtccctg ctcttctggt ccctggtcta ctgctactgc gggctctgcg cctccatcca 180

cctgctcaaa cttttgtgga gcctcggcaa ggggccggcg cagaccttcc ggcggcccgc 240
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gatcaaggat tcagggttaa gatttcacta tgttgctgct ggagaaagag gcaaaccact 360
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atttaaaagt gaatatcgag ttgtagcact ggatttgaga ggttatggag aaacagatgc 480
tcccattcat cgacagaatt ataaattgga ttgtctaatt acagatataa aggatatttt 540
agattcttta gggtatagca aatgtgttct tattggccat gactgggggg gcatgattgc 600
ttggctaatt gccatctgtt atcctgaaat ggtgatgaag cttattgtta ttaacttccc 660
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<210> 92
<211> 1021
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (971)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1004)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1008)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1010)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1018)
<223> n equals a,t,g, or c

<400> 92
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tcttgaataa tacaaatagg taagacaatt ttacaaaaat tgtgctatag aataggatat 120
ttgtgacttt ttagatgaaa tattagagct accccaccca gccacagata gcactgtaac 180
actttcttaa tagagtatag gttcaaatta taaagtccac acactggcta aaaagttcaa 240
gttcagagtt tcaatcaatt ttcattgtaa ggatgaaact gagttttact caacttgtgt 300
ctttttaaga gaatgggcca cctcccacac atcctttctc ttggactttt tttaacactt 360
ctaatgttct gtatcacgaa atcagatggc caaaacaaaa tctacaggtg ctttaaaaaa 420
gcaagtcccc aagtgattgt tacccatacc aaaatgagaa ttgctgctat aatctgttct 480

tactggamtg gccakgccaa tcttgggact aggattaaat tgcaattaaa ttckgcagtg 540
tacaaaattt ttgtcagtct gyctagaaaa agaaagagaa ctctttcatg gtagagcagt 600
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t 1021

<210> 93
<211> 1260
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (32)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (314)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (356)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (590)
<223> n equals a,t,g, or c

<400> 93
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tttaaaatta catatgtagc tcacactata aaacacagat tagaaatatt gtatagcact 180
gacctagaaa cctccattta ggtaaaacat cttaacccct ttggaagcaa aatatgttaa 240
ataacagcat aaactcccac caagaaaatc ctcaccttcc tcctttcaac acatttatta 300
tatacagctg tcantgcatt gtcaatctgc caaatggctc tatgttccaa cagggntgga 360
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<210> 94
<211> 990
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (4)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (916)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (958)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (971)
<223> n equals a,t,g, or c

<400> 94
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cccatctact tggttgtccc cagaatgggt tggcttggga gaacttgcct tgctcactcc 120
catttagact ttattagtgg agccctcctc ttgacttttg cctatttcct tgtctttcag 180
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ccttcattca ctgaatattc actcgtcctg ccaagtgcca gatgccarag tttctaaaat 900
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<210> 95
<211> 1710
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (1702)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1704)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1709)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1710)
<223> n equals a,t,g, or c

<400> 95
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gaagcttaaa agacgggatg tggggtggga gtgtgtttct taagccgaag ctgttgcagg 180
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<210> 96
<211> 781
<212> DNA
<213> Homo sapiens

<400> 96
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g 781

<210> 97
<211> 1113
<212> DNA
<213> Homo sapiens

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<210> 98
<211> 1723
<212> DNA
<213> Homo sapiens

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<210> 99
<211> 2087
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (56)
<223> n equals a,t,g, or c

<400> 99
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gggacgtagc cgccacattc cagttccgca cgcgctggga ttcggagctt cagcgggaag 240
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tatgtcactg tgtagtggat ggagtttact gtttgtggaa taaaaacggc tgtttccgtg 2040
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<210> 100
<211> 751
<212> DNA
<213> Homo sapiens

<220>

<221> SITE
<222> (663)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (702)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (705)
<223> n equals a,t,g, or c

<400> 100
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tgctccttct tctgtgatct ctgacctcga g 751

<210> 101
<211> 1223
<212> DNA
<213> Homo sapiens

<400> 101
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<210> 102
<211> 1010

<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (607)
<223> n equals a,t,g, or c

<400> 102
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<210> 103
<211> 1986
<212> DNA
<213> Homo sapiens

<400> 103
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tatgtttatt ttataatgtt ttctagtgtc aaactgtact gtggagaaaa gaaatgttag 1920
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aaaaaa 1986

<210> 104
<211> 1333
<212> DNA
<213> Homo sapiens

<400> 104
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aatgtcatct cagtgcttct attttaagat agtctctagg aatgatttaa ggactgttct 1140
catgtaaaat ccctatttct ttttttattc cattacgaat tatttgccca aaagttggat 1200
atctgtcaaa gattcataag acaagaggga gagaccctta aataagtact aaacttgtaa 1260
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aaaaaaaact cga 1333

<210> 105
<211> 944
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (889)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (896)
<223> n equals a,t,g, or c

<400> 105
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agtgtgcatt gtgctcagtc atttatttca gtgacccaaa cagagcccag tccagctgtt 180
tgtattttcc ctgcagtggg aagtggacta gggccatgtg actaagaaag ccagcctggg 240

ggctgtcttt tcacctacag atgttttaat gtgcttaaca ttatccaata ctagcaaccg 300
agatagtcta aataccacag caggatctga ttagcttttt cagatcactg cctttatttg 360
ctgtttgcaa aaaagcttaa tccagtgcta gagatcaggc ttcctgctga gccctggggt 420
agtttctctc attctttgtg ttcacagtgg caggcgttag tgagcagatt cctcctcctc 480
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ccaagggaaa aaagaagact gtctattcat accaagtagt ttccttgata tacacaaaag 600
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ttcatattta tcctactcaa tcaatctcag ttttaccaga agaattacat ttattagcca 780
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<210> 106
<211> 1172
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (904)
<223> n equals a,t,g, or c

<400> 106
ggcgggccga ggactccagc gtgcccaggt ctggcatcct gcacttgctg ccctctgaca 60
cctgggaaga tggccggccc gtggaccttc acccttctct gtggtttgct ggcagccacc 120
ttgatccaag ccaccctcag tcccactgca gttctcatcc tcggcccaaa agtcatcaaa 180
gaaaagctga cacaggagct gaaggaccac aacgccacca gcatcctgca gcagctgccg 240
ctgctcagtg ccatgcggga aaagccagcc ggagcatccc tgtgctgggc agcctggtga 300
acaccgtcct gaagcacrtc atctggctga aggtcatcac agytaacatc ctccagctgc 360
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ctggattcaa cacgcccctg gtcaagacca tcgtggagtt ccacatgacg actgaggccc 480
aagccaccat ccgcatggac accagtgcaa gtggccccac ccgcctggtc ctcagtgact 540
gtgccaccag ccatgggagc ctgcgcatcc aactgctgca taagctctcc ttcctggtga 600
acgccttagc taagcaggtc atgaacctcc tagtgccatc catgccaagg tggcccaact 660
gatcgtgctg gaagtgtttc cctccagtga agccctccgc cctttgttca ccctgggcat 720
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taacatcagc tctgatcgga tccagctgat gaactctggg attggctggt tccaacctga 840
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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aa 1172

<210> 107
<211> 427
<212> DNA
<213> Homo sapiens

<400> 107
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ggggctggct gcactgcccc aaggactttg ggaacatcaa caattgccgg atggacctct 120
acttcttcct gctggctggc attcaggccg tcacggctct cctatttgtc tggatcgctg 180
gacgctatga gagggcgtcc cagggcccag cctcccacag ccgtttcagc agggacaggg 240
gctgaacagg ccctattcca gccccctttgc ttcactctac cggacagacg gcagcagtcc 300
cagctctggt ttccttctcg gtttattctg ttagaatgaa atggttccca taaataaggg 360
gcatgagccc ttcctcaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 420
aaaaaaa 427

<210> 108
<211> 1708
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (85)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (254)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (256)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (423)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (424)
<223> n equals a,t,g, or c

<400> 108
ctcgtgcgaa ttcggcagag ctctgggcca atatggcagc gcccagcaac aagacagagc 60
tggcctggag tccgcggctg gccgngtgag taggtgattg tctgacaagc agaggcatga 120
gctgggtcca ggccacccta ctggcccgag gcctctgtag ggcctgggga ggcacctgcg 180
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aannggggcc acattgactt catctacctg gccctgcgca agatgcggga gtatggtgtc 480
gagcgggacc tggctgtgta caaccagctg ctcaacatct tccccaagga ggtcttccgg 540
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gctgtcctgg agcagatgga gaaccacggt gtgatgccca acaaggagac ggagttcctg 660
ctgattcaga tctttggacg caaaagctac cccatgctca agttggtgcg cctgaagctg 720
tggttccctc gattcatgaa cgtcaacccc ttcccagtgc cccgggacct gccccaggac 780
cctgtggagc tggccatgtt tggcctgcgg cacatggagc ctgaccttag tgccagggtc 840
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cacatcgtag gaatccagag tcccgatcag caggccgccc tggcccgcca caatccagcc 960
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gagtggaacc tctactaccc gatgcagctg gacctggagt atgtgaggag tggctgggac 1140
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tcgggctgcc agcgatgggc aggcgagacc cctccagaat ctgcaggcgc ctctggttct 1620

ccgaattcaa ataaaaaggg gcgggagcgc tgttggttgt gcgcaaaaaa aaaaaaaaaa 1680
aaaaaaaaaa aaaaaaaagg gcggccgc 1708

<210> 109
<211> 1487
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (78)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (948)
<223> n equals a,t,g, or c

<400> 109
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gcatcagcga ccagctgggg ggccaggacg tgcccgtgtt ccggaacctg tccctgctgg 180
tggtgggtgt cggcgccgtg ttctcactgc tattccacct gggcacccgg gagaggcgcc 240
ggccgcatgc ggasgagcca ggcgagcaca ccccccctgtt ggcccctgcc acggcccagc 300
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acatgaccac caggctcatc gtgaacctgt cccagaccta catggccatg tacctcacct 420
actcgctcca cctgcccaag aagttcatcg cgaccattcc cctggtgatg tacctcagcg 480
gcttcttgtc ctccttcctc atgaagccca tcaacaagtg cattgggagg aacatgacct 540
acttctcagg cctcctggtg atcctggcct ttgccgcctg ggtggcgctg gcggagggac 600
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gatgggatgg ctgcacggcg tggtgaaggt actgaacgcc acctcactgt aagacggtag 1380
attttgtatt ttaccacaat aaacaaaaca aaacaaaacc aaaaaaaaaa aaaaaaaaaa 1440
aaaaaaaagg aattcgatat caagcttatc gataccgtcg acctcga 1487

<210> 110
<211> 1525
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (78)
<223> n equals a,t,g, or c

<400> 110
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ccgcctggct cctgctgnca cctgcaggct cgtcgcgggt ggagcccacc caagacatca 120
gcatcagcga ccagctgggg ggccaggacg tgcccgtgtt ccggaacctg tccctgctgg 180

tggtgggtgt cggcgccgtg ttctcactgc tattccacct gggcacccgg gagaggcgcc 240
ggccgcatgc ggasgagcca ggcgagcaca ccccccctgtt ggcccctgcc acggcccagc 300
ccctgctgct ctggaagcac tggctccggg agcsggcttt ctaccaggtg ggcatactgt 360
acatgaccac caggctcatc gtgaacctgt cccagaccta catggccatg tacctcacct 420
actcgctcca cctgcccaag aagttcatcg cgaccattcc cctggtgatg tacctcagcg 480
gcttcttgtc ctccttcctc atgaagccca tcaacaagtg cattgggagg aacatgacct 540
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gccagggccc cctcaggacg gctggagcct ggaggagaca gccacggggt ggtgggctgg 1380
gcctggaccc caccgtggtg ggcagcaggg ctgcccggca ggcttggtgg actctgctgg 1440
cagcaaataa agagatgacg gcaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1500
aaaaaaaaaa aaacccaccg tccgc 1525

<210> 111
<211> 552
<212> DNA
<213> Homo sapiens

<400> 111
ccacgcgtcc ggtcagaatg ccttggaaaa gagctgtagt tctcctaatg ttatggttta 60
tagggcaggc catgtggctg gctcctgcct atgttctaga gtttcaagga aagaacacct 120
ttctgtttat ttggttagct ggtttgttct ttcttcttat caattgttcc atcctgattc 180
aaattatttc ccattacaaa gaagaacccc tgacagagag aatcaaatat gactagtgta 240
tgttccacac cctctgctac tgtgttacat tctgattgtc ttgtatggac cagaagagag 300
ctttgggaca ttttttctga acattctaag cattctagtg aaagttccca tgttccaaca 360
gaacttaaaa gcaatgtttg ccttatatat aaaagggaca caataattga ggtccacctt 420
ctaggaaatc ctaggactcg tttatttggg acatggtggg aataaaggtc acatattgga 480
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 540
aaaaaaaaaa aa 552

<210> 112
<211> 925
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (444)
<223> n equals a,t,g, or c

<400> 112
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tcatgttcat ggtgctggag gtggtggtga gccgggtgac ctcgtcgctg gcgatgctct 120
ccgactcctt ccacatgctg tcggacgtgc tggcgctggt ggtggcgctg gtggccgagc 180
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taatgggggc tctggtgaac gccatcttcc tgactggcct ctgtttcgcc atcctgctgg 300
aggccatcga gcgcttcatc gagccgcacg agatgcagca gccgctggtg gtccttgggg 360
tcggcgtggc cgggctgctg gtcaacgtgc tggggctctg cctcttccac catcacagcg 420

gcttcagcca ggactccggc cacngccact cgcacggggg tcacggccac ggccacggcc 480
tccccaaggg gcctcgcgtt aagagcaccc gccccgggag cagcgacatc aacgtggccc 540
cgggcgagca gggtcccgac caggaggaga ccaacaccct ggtggccaat accagcaact 600
ccaacgggct gaaattggac cccgcagacc cagaaaaccc cagaagtggt gatacagtgg 660
aagtacaagt gaatggaaat cttgtcagag aacctgacca tatggaactg gaagaagata 720
gggctggaca acttaacatg cgtggagttt ttctgcatgt ccttggagat gccttgggtt 780
cagtgattgt agtagtaaat gccttagtct tttacttttc ttggaaaggt tgttctgaag 840
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tagtactcat gcatcagttt atgag 925

<210> 113
<211> 1340
<212> DNA
<213> Homo sapiens

<400> 113
ggcacgagaa agaaaggcga gagaaaaatc aaggcaccaa atttagattg gaggtctcag 60
aggagcagtg ttttccctcc ttcgtaacag ttgaacaact tccagatgta gctagctgca 120
ccccctgtaa agatgcaggc tctttacaat gaagacacat cttctgatgt tccttctctc 180
ctgtatggcc agatgcacag gaatagtgcc caaaagacct cagcctgctt tccctttaag 240
gggaaggaga agaaaaaact ccttttttatt tttactttct ttcagcattg aatttttgtt 300
gtgtgtatgg tgacttctgt ttttgggaaa cgggaagaag ccagcagcat gctgaattgt 360
cctgacaggc tccgctgggc tcttgccgag gttagcagtg ctttttttgt atttaaacca 420
tctcccgggc agtgtaaaaa gtttgcaggt gcggacattc tgtctgactg gtctcggcag 480
tgctctataa ccctgttgtg tttcttgata aaacacagcc ccacccttta ataaagcaaa 540
gattgctatg aaaccagaga gtctattcat tactgtggag taactagagc agtctgtagt 600
gactagacat acggcaatta ggaagtcatg gagttgggat ttttgtctta attttggctg 660
ctcaaagtgc cccctgtagg atattctttt ttcgggaatt gtttccaaac ttgcctgtct 720
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cccagctact cgggaggctg aggcgggaga atcgattgga cccaggaggc ggaggttgca 1260
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aaaaaaaaaa aaaaaaaaaa 1340

<210> 114
<211> 813
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (338)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (384)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (389)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (799)
<223> n equals a,t,g, or c

<400> 114
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tagctagctg cacccccctgt aaagatgcag gctctttaca atgaagacac atcttctgat 180
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ttgaattttt gttgtgtgta tggtgacttc tgtttttngg gaaacggaag aagccagcag 360
catgctgaat tgtcctgaca ggcntccgnt ggctcttgcc gaggttagca gtgctttttt 420
tgwatttaaa ccatctcccg ggcagtgtaa aaagtttgca ggtgcggaca ttctgtctga 480
ctggtctcgg cagtgctcta taaccctgtt gtgtttcttg ataaaacaca gccccaccct 540
ttaataaagc aaagattgct atgaaaccag agagtctatt cattactgtg gagtaactag 600
agcagtctgt agtgactaga catacggcaa ttaggaagtc atggagttgg gatttttgtc 660
ttaattttgg ctgctcaaag tgccccctgt aggatattct tttttcggga attgtttcca 720
aacttgcctg tctttatcta tggtgaaact caagccgctt tttaaggcaa gcctgcaaac 780
ccaagtatca acatggggnc ctgaagggac agg 813

<210> 115
<211> 1681
<212> DNA
<213> Homo sapiens

<400> 115
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cagcccragg aagggaccca ataacctttc aaaacscaaa ctgctkcctg cggtgagggc 180
ccagggtcct ccacggagag gacaggcatc ttcctttccc accaggaagg agtcagcccg 240
gagcctctgc tatgtgcaag gcggtgtgca agcaccggct gcggctcttt gctgtctctt 300
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ctcaggggar gcccggaggc agtgctcggc acccgggaac gtgctcaggc ctcggtgggg 480
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caccacgtct tcattctcct cctggcagag ggagcacgtg gagtagacga gccgctgcag 600
ggaagggaaa gtgagcgcgt ggcacagggc tcgctgctgg aaccctgcca gggcatgcag 660
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ggagaccgcc aggaagtcct cctcagccag ytcacagcar gagacgccag cccrggccag 840
cagcgtggcc atggatgcca gccgcttggc atccaggtca aaggcaaaga tcttcccttg 900
gttcttcaga agagcagcca agtgactggt cttattgcct ggggcggcac aggcatcgat 960
gacatgggag cctggcgggg ggtccagcag catggctggg agacagctgg ccctgtcctg 1020
cagaatgagg tgtccggccc ggtacagtgg gtgttcatgc agatctgtct gggcgggaaa 1080
caccagcagc tccggcatca aggggtccag gagaaaatgc ttccccttga gggctcgtaa 1140
gtcatcgagg ctggaagccc gaccctgata ggagaaacct tgtctcttga aataatcaac 1200
tacatcatcg gagcaggtct tgagagtgtt cacacgcaca aatcgaggca gctgggaggc 1260
tggaccaggc ctggatccca cttccaacag gtcctcattc cggctcacac cccgatgaac 1320
cttgagccga gccaactcag ccttgagcct cgcctggtgc cggcccaaca gagccttcca 1380
tcggcccca ccccctcgaa agcccctttcc caacaacaac tcatacacta gcaccttggc 1440
caggtgcggc cgcagcttct tctccgcacg gaggaggccg gcgctggcga tcacagcatc 1500
cagcacggcg gagtagcgct gcgtttcgca caccagcgcg tacagctgct tcacgttctg 1560
gaagttgctg gagtacacca acccctgat agagcctggc ggctctccac gccggccaac 1620
acgcctgcag ctgcagcata cagccccatg ttccgtcgcg ctttacggct ttgtggcaaa 1680
a 1681

<210> 116

<211> 2052
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (2045)
<223> n equals a,t,g, or c

<400> 116
tttgcttttc aaatgctccc aaggtctcag atgaagcggt gaaaaaagat tcagagttgg 60
ataagcactt ggaatcacgg gttgaagaga ttatggagaa gtctggcgag gaaggaatgc 120
ctgatcttgc ccatgtcatg cgcatcttgt ctgcagaaaa tatcccaaat ttgcctcctg 180
ggggaggtct tgctggcaas cgtaatgtta ttgaagctgt ttatagtaga ctgaatccac 240
atagagaaag tgatgggggt gctggagatc tagaagaccc atggtagcct taaaaacctt 300
ctaaaatgct tttrattctg aaaattgggg gaaaaaactt ttaatcacaa ttttcttcaa 360
tacaagggga aaatattctt gcggattccc aacgttttgt gatatgagca gaaaatcatt 420
agcatttccc atcatttgtt catatttgtg ttttctgaca gttgccactt gtagcattgc 480
ctgtactaca gtatttttg ccaacctcag gcatactcgt tacatctgta ttgaactttc 540
ggccctagaa accagtggag ttatttcacc acaaatcaac aatgtgcctg aggtgcatgg 600
gaaatatagt tagctatact ctgaaaatac attatgtttt ttttctttaa acaaaacaca 660
caacatgtaa gcatgtaaga gtaaagaatt gtatgatatg ttccttttt cagttcacca 720
agttggaagc cttttgcagc tctgtggctt ggaatttcat ttgagcaatt tctataggat 780
atgtatttat tattgattgt tatttaawtt ttttcccaat tttacctgta ttaccaaact 840
gggttctcca ataatgtcca aattgtaatg ttgccttgct tcaagataaa gtgtatttgg 900
gaataatatt ataaaccctt acaaatttta tgcatgtatc tactgcatcc ttcaactctc 960
actagaaaat cttttgaaac caaatggatt aatttatggc tatttataat ttgctttgac 1020
atctcactgt tggaaatttt ttaaagatga gatttgcctt tataatgtaa attgtgattt 1080
ttgttttaca tgtgggtttc tatagtttta atttttcag cttttaagat acgagttttg 1140
tgtaatttgg tatttttaat catttatgtt attttaaaag ctcagaatat cacattgaaa 1200
ttactataaa tacatttaaa attatctatt ttagatctaa ggaaatacta cagagatatt 1260
ttcatgggtt cagtaacttt tcattttata acattgggca cggtacagag tgattgtcac 1320
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gagttttgca tgtattaaat tcaattaatg ctgaacatga agagtaaagt atttatctga 1440
aagaagtttc tgggttagga gaagtaatga atgtatccat ttgtacatgg tttacatgtt 1500
gtggatgctt tgtaaacatt ttcctgtatg tttaaattgt gtttcagcag gatgtaattg 1560
cccttgtgtg tagttaaaat gagtcatcat ctggtccttt gtgaaatgga attcatggta 1620
ttttctgtaa cgttttcctg aagctgtttc tggagagcca cacatttaaa tacagacagc 1680
tttcctgatc atttgattta ttgtgcacct gatttttggt ctaaaaggaa ttattgccac 1740
aatatatttt atttattctt tagattttag ccttgtaagt taaagtgctt tacatgatga 1800
tgtgaaaagc tgtttgtccc tttactgggt ttgggggggtt gttaaaagat agggaatgaa 1860
gaatgcaaaa tggtttatcg ttcaaactgt ccactctgat ccaaccctgt actgatagta 1920
cttcccagta tgatattgtg atgtttcata caatgcagtg aacataacca acttgttacc 1980
taaataaaga attgataaaa acagtgtgac atattaaaaa aaaggggggc ccggtaccca 2040
attcncccta ta 2052

<210> 117
<211> 539
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (528)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (529)

<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (531)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (532)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (537)
<223> n equals a,t,g, or c

<400> 117
gagatacatt ccatgaatac ctagtttatt gagagttttt agcatgaagg actgtcgaat 60
tttgtcaaag gctttttctg catctattga gataatcatg tggtttttgt ctttggttct 120
gtttatgtga tggactatgt ttattgattt gcatatgttg aaccagcctt gcatctcagg 180
gatgaagcca actcgatcgt tgtggataag ctttttgatg tgctgctgga tttggtttgc 240
caatatttta ttgaggattt ttgcatcagt gttcttcagg gatattggtc taaaattctc 300
tttttttttgt tgtgtctctg ccaggctttg gtatcaggat gatgctggcc tcataaatga 360
gttagggagg attccctctt tctattgatc agaatagttt cagaaggaat ggtaccagct 420
cttctttgta cctctggtag aatttgggtg kgaatctatc ttgkcctgga atatttttgg 480
ggttggaact caaaaaaaaa aaaaaaaaaa tcaaaaaaaa aaaaaaanna nnaaaanaa 539

<210> 118
<211> 882
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (117)
<223> n equals a,t,g, or c

<400> 118
gaattcggca cgagcagacc tgggctcgag accataactg tttggcttta acagtacgtg 60
ggcggccgga atccgggagt ccggtgaccc gggctgtggt ctagcataaa ggcggancca 120
gaagaagggg cggggtatgg gagaagcctc cccacctgcc cccgcaaggc ggcatctgct 180
ggtcctgctg ctgctcctct ctaccctggt gatcccctcc gctgcagctc ctatccatga 240
tgctgacgcc caagagagct ccttgggtct cacaggcctc cagagcctac tccaaggctt 300
cagccgactt ttcctgaaag taacctgctt cggggcatag acagcttatt ctctgccccc 360
atggacttcc ggggcctccc tgggaactac cacaaagagg agaaccagga gcaccagctg 420
gggaacaaca ccctctccag ccacytccag atcgacaaga tgaccgacaa caagacagga 480
gaggtgctga tctccgagaa tgtggtggca tccattcaac cagcggaggg gagcttcgag 540
ggtgatttga aggtacccag gatggaggag aaggaggccc tggtacccat ccagaaggcc 600
acggacagct tccacacaga actccatccc cgggtggcct tctggatcat taagctgcca 660
cggcggaggt cccaccagga tgccctggag ggcggccact ggctcagcga gaagcgacac 720
cgcctgcagg ccatccggga tggactccgc aaggggaccc acaaggacgt cctagaagag 780
gggaccgaga gctcctccca ctccaggctg tccccccgaa agacccactt actgtacatc 840
ctcaggccct ctcggcagct gtaggggtgg ggaccgggga gc 882

<210> 119
<211> 1193
<212> DNA
<213> Homo sapiens

<400> 119
acactatata agttacgcct gcaggttacc ggtccggtaa ttcccgggtc gtacccacgc 60
gtccggtaat gtcaaaggaa aagtaattct gtcaatgctg gttgtctcaa ctgtgatcat 120
tgtgttttgg gaatttatca acagcacaga aggctctttc ttgtggatat atcactcaaa 180
aaacccagaa gttgatgaca gcagtgctca gaagggctgg tggtttctga gctggtttaa 240
caatgggatc cacaattatc aacaagggga agaagacata gacaaagaaa aaggaagaga 300
ggagaccaaa ggaaggaaaa tgacacaaca gagcttcggc tatgggactg gtttaatcca 360
aacttgaagg aatccgaata actaaactgg actctggttt tctgactcag tccttctaga 420
agacctggac tgagagatca tgcggttaag gagtgtgtaa caggcggacc acctgttggg 480
actgsgagat tctcaagggg aaggactggg tctcatttct cccatctcag cgcttagcag 540
gatgacctgg tatagagcag ggaactggga aatgtgggtc aggggatcag acactccagt 600
tgggtctttt atataaatta aatggcaaaa ggctccatac ccttctcctt ctttcctacc 660
ctccacttta tctgcaaaat gggaatgatg ataacaccca cttcatagaa tggtcatgaa 720
gatcaaatga gagaataaaa gtcaagcact tagcctctgg tgcacaataa gtattaaata 780
agtataccta ttcctccttt tccttttttа aaaataatat taccaaatgt ccagcttata 840
cacatttaca agacttagct agtgggctat gttagagcta ctaaaagatc tttgacaagc 900
taaaactaag atgcaatgaa tgaggtgtaa cgaacaagag agttttaagt tcagaaatgg 960
ttacagaagt ataagacagc tgtgtgggtg ttttttggtt tttggtttct ggtttacaat 1020
ctcgtcattc aacaaagatg ggagttttat agaactaaaa gcmccatgta agctactaaa 1080
aacaacaaca aaaaaggctc atcatttctc agtctgaatt gacaaaaatg ccaatgcaaa 1140
taaaaatgat tacttttttat tttaaaaaaa aaaaaaaaaa aaaaaaactc gta 1193

<210> 120
<211> 1338
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (519)
<223> n equals a,t,g, or c

<400> 120
ggcacgaggg tgaggcccag gtagcgtttg caatccagcc ccaccgtcac ctcttttctt 60
ggacttctag ttttcctcac ccctattgcc ttcatccttt tacctccgat cctgtggagg 120
gaatgagctg gagccttgtg gcacaatttg tgaggggctc tttatctcca tggcattcaa 180
actcctcatt ctgctcatag ggacctgggc actttttttc cgcaagcgga gagctgacat 240
gccacgggtg tttgtgtttc gtgccctttt gttggtcctc atctttctct tttgtggttt 300
ccctattggc ttttttacgg ggtccgcatt ttggactctc gggaaccgga attaccaagg 360
gattgtgcaa tatgcagtct ccccttgtgg aatgccctcc tccttccatc cattactggc 420
catccgtccc tgctggagct cagggagctt gcagcccaat gttccacgct gcaggttggt 480
cccgctccca accgaatggg gaaatccccg cttccagcnt gggacacctg agtatccagc 540
gagcagcatt ggtggtccta gaaaattact acaaagattt caccatctat aacccaaacc 600
tcctaacagc ctccaaattc cgagcagcca agcatatggc cgggctgaaa gtctacaatg 660
tagatggccc cagtaacaat gccactggcc agtcccgggc catgattgct gcagctgctc 720
ggcgcaggga ctcaagccac aacgagttgt attatgaaga ggccgaacat gaacggcgag 780
taaagaagcg gaaagcaagg ctggtggttg cagtggaaga ggccttcatc cacattcagc 840
gtctccaggc tgaggagcag cagaaagccc caggggaggt gatggaccct agggaggccg 900
cccaggccat tttcccctcc atggccaggg ctctccagaa gtacctgcgc atcacccggc 960
agcagaacta ccacagcatg gagagcatcc tgcaagcacc tggccttctg catcaccaac 1020
ggcatgaccc ccaaggcctt cctagaacgg tacctcagtg cgggccccac cctgcaatat 1080
gacaaggacc gctggctctc tacacagtgg aggcttgtca gtgatgaggc tttgactaat 1140
ggattacggg atggaattgt gttcgtcctt aagtgcttgg acttcagcct cgtagtcaat 1200
gtgaagaaaa ttccattcat catactctct gaagagttca tagaccccaa atctcacaaa 1260
tttgtccttc gcttacagtc tgagacatcc gtttaaaagt tctatatttg tggctttatt 1320
aaaaaaaaaa aaaaaaaa 1338

<210> 121

<211> 1183
<212> DNA
<213> Homo sapiens

<400> 121
tgcaggaatt cggcacgagc tggctgcagg gtctctgggg agagaagggg cctcggcttc 60
acaggatggg gctgccagtg tcctgggccc ctcctgccct ctgggttcta gggtgctgcg 120
ccctgctcct ctcgctgtgg gcgctgtgca cagcctgccg cagcccgagg acgctgtagc 180
ccccaggaag agggcgcgga ggcagcgggc gaggctgcag ggcagtgcga cggcggcgga 240
agcgtcccta ctgaggcgga cccacctctg cttccctcag caagtcggac accagactgc 300
acgagctgca ccggggcccg cgcagcagca gggccctgcg gcctgccagy atggatctcc 360
tgcgcccaca ctggctggag gtgtccaggg acatcaccgg accgcaggca gccccctctg 420
ccttcccaca ccaggagctg ccccgggctc tgccggcagc tgcagccacc gcaggtgcgc 480
tggcctcgag gccacctatt ccaacgtggg gctggcggcc cttcccgggg tcagcctggc 540
ggccagccct gtggtggccg agtatgcccg cgtccagaag cgcaaaggga cccatcgcag 600
tccccaagag ccacagcagg ggaagactga ggtgaccccg gccgctcagg tggacgtcct 660
gtactccagg gtctgcaagc ctaaaaggag ggacccagga cccaccacag acccgctgga 720
ccccaagggc cagggagcga ttctggccct ggcgggtgac ctggcctacc agaccctccc 780
gctcagggcc ctggatgtgg acagcggccc cctggaaaac gtgtatgaga gcatccggga 840
gctgggggac cctgctggca ggagcagcac gtgcggggct gggacgcccc ctgcttccag 900
ctgccccagc ctagggaggg gctggagacc cctccctgcc tccctgccct gaacactcaa 960
ggacctgtgc tccttcctcc agagtgaggc ccgtcccccg ccccgccccg cctcacagct 1020
gacagcgcca gtcccaggtc cccgggccgc cagcccgtga ggtccgtgag gtcctggccg 1080
ctctgacagc cgcggcctcc ccgggctcca gagaaggccc gcgtctaaat aaagcgccag 1140
cgcaggatga aagcgaaaaa aaaaaaaaaa aaagggcggc cgc 1183

<210> 122
<211> 615
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (18)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (20)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (584)
<223> n equals a,t,g, or c

<400> 122
cctgtatata aaattggncn ctatggtccc gtacaatgaa gaaatgcaaa gatagttaag 60
aaagactcgg ccttcaagga gcctaaatgt gtagaaaagg actaaggcaa aacaataact 120
tttttgagct cttgccatgt gtgaagcact ttatacacct gtaaggtagg taacgttgtt 180
cttattaaac atgaagaaaa tgagactttg tgagaagcaa tacagtatag aagttaagaa 240
tatggactct aaagctagat ttcagaggtt tgaagtagct ctgctactta ctggctgtgt 300
gactttgagc agattactta acctgtctgt gcctatgttt acttttattg ttgtaaaaag 360
atatgcaaca taaaatattc catttcaacc gtttttacgt gtatacttca ctgacattag 420
ttgcattcac tatgttgtgc aaacgtaggg tcgctatgaa gattaaatga gttaattcat 480
ataaagccct cagaagagtg tctggcacat ggtgagtatt ggctgtactg tggtcgatgt 540
cattgttaga gagctttagt gatttgctta agacagaaag gtanactggg gtgcggtggg 600
ctcacgccct ggtta 615

<210> 123
<211> 587
<212> DNA
<213> Homo sapiens

<400> 123
cccacgcgtc cgcctggaac ctgattctcc tgaccgtctt taccctgtcc atggcctacc 60
tcactgggat gctgtccagc tactacaaca ccacctccgt gctgctgtgc ctgggcatca 120
cggcccttgt ctgcctctca gtcaccgtct tcagcttcca gaccaagttc gacttcacct 180
cctgccaggg cgtgctcttc gtgcttctca tgactctttt cttcagcgga ctcatcctgg 240
ccatcctcct acccttccaa tatgtgccct ggctccatgc agtttatgca gcactgggag 300
cgggtgtatt tacattgttc ctggcacttg acacccagtt gctgatgggt aaccgacgcc 360
actcgctgag ccctgaggag tatatttttg gagccctcaa catttaccta gacatcatct 420
atatcttcac cttcttcctg cagcttttg gcactaaccg agaatgagga gccctccctg 480
ccccaccgtc ctccagagaa tgcgcccctc ctggttccct gtccctcccc tgcgctcctg 540
cgagaccaga tataaaacta gctgccaacc caaaaaaaaa aaaaaaa 587

<210> 124
<211> 1379
<212> DNA
<213> Homo sapiens

<400> 124
gggcccagca gcagcggcac ctggagaagc agcacctgcg aattcagcat ctgcaaagcc 60
agtttggcct cctggaccac aagcacctag accatgaggt ggccaagcct gcccgaagaa 120
agaggctgcc cgagatggcc cagccagttg acccggctca caatgtcagc cgcctgcacc 180
ggctgcccag ggattgccag gagctgttcc aggttgggga gaggcagagt ggactatttg 240
aaatccagcc tcaggggtct ccgccatttt tggtgaactg caagatgacc tcagatggag 300
gctggacagt aattcagagg cgccacgatg gctcagtgga cttcaaccgg ccctgggaag 360
cctacaaggc ggggtttggg gatccccacg gcgagttctg gctgggtctg gagaaggtgc 420
atagcatcat gggggaccgc aacagccgcc tggccgtgca gctgcgggac tgggatggca 480
acgccgagtt gctgcagttc tccgtgcacc tgggtggcga ggacacggcc tatagcctgc 540
agctcactgc acccgtggcc ggccagctgg gcgccaccac cgtcccaccc agcggcctct 600
ccgtaccctt ctccacttgg gaccaggatc acgacctccg cagggacaag aactgcgcca 660
agagcctctc tggaagctgg tggtttggca cctgcagcca ttccaacctt caacgggcca 720
gtacttccgg ctccatccca cagcagcggc agaagcttaa gaagggaatc ttctggaaga 780
cctgcgggcc gctactaccc gctgcaggcc accaccatgt tgatccagcc catggcagca 840
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ttggctctgc ccgaggatgt ggccgttccc tgcctgggca ggggctccaa ggaggggcca 960
tctggaaact tgtggacaga gaagaagacc acgactggag aagccccctt tctgagtgca 1020
gggggctgc atgcgttgcc tcctgagatc gaggctgcag gatatgctca gactctagag 1080
gcgtggacca aggggcatgg agcttcactc cttgctggcc agggagttgg ggactcagag 1140
ggaccacttg gggccagcca gactggcctc aatggcggac tcagtcacat tgactgacgg 1200
ggaccagggc ttgtgtgggt cgagagcgcc ctcatggtgc tggtgctgtt gtgtgtaggt 1260
cccctgggga cacaagcagg cgccaatggt atctgggcgg agctcacaga gttcttggaa 1320
taaaagcaac ctcagaacac ttaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaa 1379

<210> 125
<211> 1268
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (1184)
<223> n equals a,t,g, or c

<220>
<221> SITE

<222> (1240)
<223> n equals a,t,g, or c

<400> 125
agggttgatg ggttatggtc aggagtccca gctgggccca ccacctcctc aggaaggcgg 60
gtgaggttgg tgtgagactg acggtgcctc ctcatgtccc cttggagcgc cccaccccac 120
atctcccggc ctcgggtcct tgcctggccc agcatgagag gtgcttcata ggaacggagg 180
gaggacatgt cgggacagct cgatgctcgg cctgctgctg ctctgcaccc ccagggcctg 240
gctcaccctc tctggacctg tctgcttcca aggaagggac cctctgaggt cccacagagg 300
ccaccccagc tgtgggtcgt gagcatctct gtcttgcagg gacagcatcg tggccgagct 360
ggaccgagag atgagcagag cgtggacgtg accaacacca ccttcctgct catggccgcc 420
tccatctatc tccacgacca gaacccggat gccgccctgc gtgcgctgca ccagggggac 480
agcctggagt ggtgagtggc ctccctgctc tgggccagcc cagggaggca agtgcccctt 540
gccacatctc caggctgcgc acggcctcgc tggctgtcgt catgggagca gagaaaggtg 600
gtgctgaaat gaggccctgg cctgctgtcc aggctccagc tcccctgccc agtgtgggag 660
gcactcccat ctgcgcacca ggctgcggat ccaaggacac ggtgcccagg ctgcaaccct 720
ctgttcccaa gggcagagca gaaagcggct ttgtctctgc tcggtttctg tgtccccacc 780
ccccacgaag ccttctgtgt ctcggccctg ggcccagtct ctcaggcctc cccgggcccc 840
ccataccggc cctcctccag ggccctctgg ggttggggtg ctgaagccct gcaaggttgg 900
tgccccctc caccctagga tgtgactccg ggccatgtcc agggcactgg tcacagaaag 960
tgtgtcagtt cttccccgtg agctgtccct gcagtgcctg ccttccactg tgagttgcaa 1020
gctgggcatt tcatggtcgc tgtggatctg ctcccatccc acctccatcc acagagggct 1080
tagaattgca gggcgagcca ggcatggtga catgcaccta tgtttccagc tacttgggag 1140
gcggaagtca ggagtatccc ttgagtctgg gaggtggagg ctgncagtga gccgtgatgg 1200
tgccactgca ctccagcctg ggtggcagag ccagaccctn actcacacac aaaaaaaaaa 1260
aaaaaaaa 1268

<210> 126
<211> 1311
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (1036)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1112)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1168)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1223)
<223> n equals a,t,g, or c

<400> 126
gaaaaaagaa agcaatatgg aaaccgaact aaggagattt taaactgaga tataagatgc 60
tttcaattat tcccaatgac aggctattta tcaatttaat atttttaagc aacttcctcc 120
catcagtgct ctgggaacca gctgggcaga tgtggtacac ccatgtcaga taccccagtg 180
gcaggctcct gtcactgtag cacttggtcc ctccatccct cccagccttc ctagctcctt 240
gctcctggaa acctcccccc atcaatctct gacatttcag aggaaatact gtttgtcacc 300
tcttaaggaa tctgggagga cggcctgtga gatatggcgt cagttacagc ctcttaaaga 360

gtcaatagcc cctgcagagg ccagaacact ggaacaaatg taaggaaggt atagttttta 420
aagatttttg acttgaatta aataggattg gttacttctt gcccctcccg agggtggact 480
gtgcacagaa gagacctctt caccgggttt gctgctcttt ttcgcactgt gagttggggt 540
tctaacagtc agcgttggtc cataacaaaa tggaaatcct ttctttcccc tcctgttaat 600
gccccctgtc tgtgcagtga ctgtgcaacc agcacctttt gtggtcgaat cagccagcag 660
aagtgcccct cgtgttcctg gattctctct tctgtggttc catttctttg agtcctgggt 720
tctcgccctg aatggctcaa caggggaaa ggcagacagc ttcttcgtgc cagaaacatt 780
ttttttttt tttgaaatar tgagccaaga ttgcgccact gcattccatc ctcagcaaca 840
garcaagact ccaactcawa acaaaacaaa agattgargt wattgtggca acacctgcct 900
ttttttctaa gctgcaattc tctactgttt tcaagaaaaa tacaagttag cctatttaca 960
gaatgttttg aattgactcc tgtcctctgg ttaaaactcc tcttgagata attgatagct 1020
gaaaaggtag gatggntctc tcaaacttga cttccatcta aatcaacgct gagttgatta 1080
acttagatat caagaaaaat tgcctcatta gnttacccct gaggagatgc ctatgaaggt 1140
acatcctttt tacaattaat aagacagntt tcacatgaag aaacaatttg aaatatttaa 1200
taagaaaatg gggtgaaggc aancattacg gttgggaaaa gaccatgcaa gcctttatag 1260
aggataacga tttatatatt cactattaat ttggccgggt aataggaacc t 1311

<210> 127
<211> 1249
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (1217)
<223> n equals a,t,g, or c

<400> 127
ggccaggcgg gtctcaaact cctcgtctca ggtgatctgc ttgcctcggc ctcccaaagt 60
gctgggatta caggcgtgag cactgcgccc agcctgagtt tcatttttta agtcacatag 120
cagtagtcct tatttcagtg ctagaccctt tgaaatgcga tgaaagctat atggaccctt 180
cgctttgtta tataacatat gcacacatac ccagaatttt gcacatatgt tcagagattc 240
ctagacctgc agacctgcct ctgtgtgtcc caatttaaga acctctgttc tttcttcatg 300
actggatttg cccaattttg tgttattttg ggacttaatt tgtccctctt tgggacattt 360
ccttatttat tgccctcttc agagagtaga tgtagaaaat aaagagagga aacctagatt 420
acttaatttt aatttaacat tttctataga tagcatacca cgccaagtgt gctctgtctt 480
gatccccttc tttctagcat ctgccagaca ttgtagagtt tcscaascag ttgtaggttt 540
gagctgcagc cagtcatttc ttttattctt taaaagtaca tagatttgtc tttttagggc 600
tttactgaaa gtaaaatatc ctgacattta aactgacaga tgtaggaggt aaaaaataga 660
gttctgaaac atwtgaattt atgtgacagc tgaagtcacg agatgaggka tgtatgtccc 720
ccagggaggw tgcagaaaga agaaaagggt actggaaaca gcatgtcagt ggtgccagct 780
gagggctgga ggcagccagg agagttggga gcctgggtgc tgggtggaga gaggttaaca 840
gggaakacat gggaagtatt gtgaaggctg gtgtgagcag gggactactc cagccctgtt 900
ggaacataga gccatttggc agattgacaa tgcagtgaca gctgtatata ataaatgtgt 960
tgaaaggagg aaggtgagga ttttcttggt gggagtttat gctgttattt aacatatttt 1020
gcttccaaag gggttaagat gttttaccta aatggargtt tctaggtcag tgctatacaa 1080
tatttctaat ctgtgtttta tagtgtgagc tacatatgta attttaaaat tttcaagtag 1140
ccacataata aaggaaacag gtgaaattta aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1200
aaaaaaaaaa aaaaaanaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaa 1249

<210> 128
<211> 1660
<212> DNA
<213> Homo sapiens

<400> 128
ccgggtcgac ccacgcgtcc ggcccgcgga aggcgacatg ggctccgctc cctgggcccc 60
ggtcctgctg ctggcgctcg ggctgcgcgg cctccaggcg ggggcccgca gcggaccccg 120
gcttccagga gcgcttcttc cagcagcgtc tggaccactt caacttcgag cgcttcggca 180

acaagacctt ccctcagcgc ttcctggtgt cggacaggtt ctgggtccgg ggcgaggggc 240
ccatcttctt ctacactggg aacgagggcg acgtgtgggc cttcgccaac aactcggcct 300
tcgtcgcgga ctggcggccg agcgggggcc tctactggtc ttcgcggagc accgctacta 360
cgggaagtcg ctgccgttcg gtgcgcagtc cacgcagcgc gggcacacgg agctgctgac 420
ggtggagcag gccctggccg acttcgcaga gctgctccgc gcgctacgac gcgacctcgg 480
ggcccaggat gcccccgcca tcgccttcgg tggaagttat ggggggatgc tcagtgccta 540
cctgaggatg aagtatcccc acctggtggc gggggcgctg gcggccagcg cgcccgttct 600
atctgtggca ggcctcggcg actccaacca gttcttccgg gacgtcacgg cggactttga 660
gggccagagt cccaaatgca cccagggtgt gcgggaagcg ttccgacaga tcaaggactt 720
gttcctacag ggagcctacg acacggtccg ctgggagttc ggcacctgcc agccgctgtc 780
agacgagaag gacctgaccc agctcttcat gttcgcccgg aatgccttca ccgtgctggc 840
catgatggac tacccctacc ccactgactt cctgggtccc ctccctgcca accccgtcaa 900
ggtgggctgt gatcggctgc tgagtgaggc ccagaggatc acggggctgc gagcactggc 960
agggctggtc tacaacgcct cgggctccga gcactgctac gacatctacc ggctctacca 1020
cagctgtgct gaccccactg gctgcggcac cggccccgac gccagggcct gggactacca 1080
ggcctgcacc gagatcaacc tgaccttcgc cagcaacaat gtgaccgata tgttcccgga 1140
cctgcccttc actgacgagc tccgccagcg gtactgcctg gacacctggg gcgtgtggcc 1200
ccggcccgac tggctgctga ccagcttctg gggggggtgat ctcagagccg ccagcaacat 1260
catcttctcc aacgggaacc tggacccctg ggcaggggggc gggattcgga ggaacctgag 1320
tgcctcagtc atcgccgtca ccatccaggg gggagcgcac cacctcgacc tcagagcctc 1380
ccacccagaa gatcctgctt ccgtggttga ggcgcggaag ctggaggcca ccatcatcgg 1440
cgagtgggta aaggcagcca ggcgtgagca gcagccagct ctgcgtgggg ggcccagact 1500
cagcctctga gcacaggact ggaggggtct caaggctcct catggagtgg gggcttcact 1560
caagcagctg gcggcagagg gaaggggctg aataaacgcc tggaggcctg gccatgtaaa 1620
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1660

<210> 129
<211> 2075
<212> DNA
<213> Homo sapiens

<400> 129
ccacgcgtcc gtggggccga gcgccgctgg gtaggcggaa gtagccgcag atggcggcgg 60
ctatgccctt gctctgctcg tcctgttgct cctggggccc ggcggctggt gccttgcaga 120
acccccacgc gacagcctgc gggaggaact tgtcatcacc ccgctgcctt ccggggacgt 180
agccgccaca ttccagttcc gcacgcgctg ggattcggag cttcagcggg aaggagtgtc 240
ccattacagg ctctttccca aagccctggg gcagctgatc tccaagtatt ctctacggga 300
gctgcacctg tcattcacac aaggcttttg gaggacccga tactgggggc caccttcct 360
gcaggcccca tcagacactg accactactt tctgcgctat gctgtgctgc cgcgggaggt 420
ggtctgcacc gaaaacctca ccccctggaa gaagctcttg ccctgtagtt ccaaggcagg 480
cctctctgtg ctgctgaagg cagatcgctt gttccacacc agctaccact cccaggcagt 540
gcatatccgc cctgtttgca gaaatgcacg ctgtactagc atctcctggg agctgaggca 600
gaccctgtca gttgtatttg atgccttcat cacggggcag ggaaagaaag actggtccct 660
cttccggatg ttctcccgaa ccctcacgga gccctgcccc ctggcttcag agagccgagt 720
ctatgtggac atcaccacct acaaccagga caacgagaca ttagaggtgc acccaccccc 780
gaccactaca tatcaggacg tcatcctagg cactcggaag acctatgcca tctatgactt 840
gcttgacacc gccatgatca acaactctcg aaacctcaac atccagctca agtggaagag 900
acccccagag aatgaggccc ccccagtgcc cttcctgcat gcccagcggt acgtgagtgg 960
ctatgggctg cagaaggggg agctgagcac actgctgtac aacacccacc cataccgggc 1020
cttcccggtg ctgctgctgg acaccgtacc ctggtatctg cggctgtatg tgcacaccct 1080
caccatcacc tccaagggca aggagaacaa accaagttac atccactacc agcctgccca 1140
ggaccggctg caaccccacc tcctggagat gctgattcag ctgccggcca actcagtcac 1200
caaggtttcc atccagtttg agcgggcgct gctgaagtgg accgagtaca caccagatcc 1260
taaccatggc ttctatgtca gcccatctgt cctcagcgcc cttgtgccca gcatggtagc 1320
agccaagcca gtggactggg aagagagtcc cctcttcaac agcctgttcc cagtctctga 1380
tggctctaac tactttgtgc ggctctacac ggagccgctg ctggtgaacc tgccgacacc 1440
ggacttcagc atgccctaca acgtgatctg cctcacgtgc actgtggtgg ccgtgtgcta 1500
cggctccttc tacaatctcc tcacccgaac ctttccacat cgaggagccc cgcacaggtg 1560
gcctggccaa gcggctggcc aaccttatcc ggcgcgcccg agtgtccccc ccactctgat 1620

tcttgccctt tccagcagct gcagctgccg tttctctctg gggaggggag cccaagggct 1680
gtttctgcca cttgctctcc tcagagttgg cttttgaacc aaagtgccct ggaccaggtc 1740
agggcctaca gctgtgttgt ccagtacagg agccacgagc caaatgtggc atttgaattt 1800
gaattaactt agaaattcat ttcctcacct gtagtggcca cctctatatt gaggtgctca 1860
ataagcaaaa gtggtcggtg gctgctgtat tggacagcac agaaaaagat ttccatcacc 1920
acagaaaggt cggctggcag cactggccaa ggtgatgggg tgtgctacac agtgtatgtc 1980
actgtgtagt ggatggagtt tactgtttgt ggaataaaaa cggctgtttc cgtggttaaa 2040
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaa 2075

<210> 130
<211> 56
<212> PRT
<213> Homo sapiens

<400> 130
Met Ala Lys Thr Asp Phe Ser Ile Ile Leu Leu Lys Leu His Cys Leu
1 5 10 15

Phe Phe Phe Ser Val Ile Ser Val His Cys Ala Gln Ser Phe Ile Ser
20 25 30

Val Thr Gln Thr Glu Pro Ser Pro Ala Val Cys Ile Phe Pro Ala Val
35 40 45

Gly Ser Gly Leu Gly Pro Cys Asp
50 55

<210> 131
<211> 42
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (3)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (42)
<223> Xaa equals stop translation

<400> 131
Met Ala Xaa Leu Asp Asn Cys Leu Met Leu Leu Ile Thr Ser Gly Thr
1 5 10 15

Trp Leu Gly Ser Val Ala Arg Lys Thr Trp Gln Ala Ile Cys Asp Ser
20 25 30

Gly Ser Ser Gly Cys Ala Leu Ile Arg Xaa
35 40

<210> 132
<211> 415
<212> PRT
<213> Homo sapiens

<220>
<221> SITE

<222> (415)
<223> Xaa equals stop translation

<400> 132

```
Met Asn Pro Thr Leu Gly Leu Ala Ile Phe Leu Ala Val Leu Leu Thr
  1               5                  10                  15

Val Lys Gly Leu Leu Lys Pro Ser Phe Ser Pro Arg Asn Tyr Lys Ala
             20                  25                  30

Leu Ser Glu Val Gln Gly Trp Lys Gln Arg Met Ala Ala Lys Glu Leu
         35                  40                  45

Ala Arg Gln Asn Met Asp Leu Gly Phe Lys Leu Leu Lys Lys Leu Ala
     50                  55                  60

Phe Tyr Asn Pro Gly Arg Asn Ile Phe Leu Ser Pro Leu Ser Ile Ser
 65                  70                  75                  80

Thr Ala Phe Ser Met Leu Cys Leu Gly Ala Gln Asp Ser Thr Leu Asp
                 85                  90                  95

Glu Ile Lys Gln Gly Phe Asn Phe Arg Lys Met Pro Glu Lys Asp Leu
            100                 105                 110

His Glu Gly Phe His Tyr Ile Ile His Glu Leu Thr Gln Lys Thr Gln
        115                 120                 125

Asp Leu Lys Leu Ser Ile Gly Asn Thr Leu Phe Ile Asp Gln Arg Leu
    130                 135                 140

Gln Pro Gln Arg Lys Phe Leu Glu Asp Ala Lys Asn Phe Tyr Ser Ala
145                 150                 155                 160

Glu Thr Ile Leu Thr Asn Phe Gln Asn Leu Glu Met Ala Gln Lys Gln
                165                 170                 175

Ile Asn Asp Phe Ile Ser Gln Lys Thr His Gly Lys Ile Asn Asn Leu
            180                 185                 190

Ile Glu Asn Ile Asp Pro Gly Thr Val Met Leu Leu Ala Asn Tyr Ile
        195                 200                 205

Phe Phe Arg Ala Arg Trp Lys His Glu Phe Asp Pro Asn Val Thr Lys
    210                 215                 220

Glu Glu Asp Phe Phe Leu Glu Lys Asn Ser Ser Val Lys Val Pro Met
225                 230                 235                 240

Met Phe Arg Ser Gly Ile Tyr Gln Val Gly Tyr Asp Asp Lys Leu Ser
                245                 250                 255

Cys Thr Ile Leu Glu Ile Pro Tyr Gln Lys Asn Ile Thr Ala Ile Phe
            260                 265                 270

Ile Leu Pro Asp Glu Gly Lys Leu Lys His Leu Glu Lys Gly Leu Gln
        275                 280                 285

Val Asp Thr Phe Ser Arg Trp Lys Thr Leu Leu Ser Arg Arg Val Val
```

290 295 300

Asp Val Ser Val Pro Arg Leu His Met Thr Gly Thr Phe Asp Leu Lys
305 310 315 320

Lys Thr Leu Ser Tyr Ile Gly Val Ser Lys Ile Phe Glu Glu His Gly
325 330 335

Asp Leu Thr Lys Ile Ala Pro His Arg Ser Leu Lys Val Gly Glu Ala
340 345 350

Val His Lys Ala Glu Leu Lys Met Asp Glu Arg Gly Thr Glu Gly Ala
355 360 365

Ala Gly Thr Gly Ala Gln Thr Leu Pro Met Glu Thr Pro Leu Val Val
370 375 380

Lys Ile Asp Lys Pro Tyr Leu Leu Leu Ile Tyr Ser Glu Lys Ile Pro
385 390 395 400

Ser Val Leu Phe Leu Gly Lys Ile Val Asn Pro Ile Gly Lys Xaa
405 410 415

<210> 133
<211> 45
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (45)
<223> Xaa equals stop translation

<400> 133
Met Gly Gln Gln Ser Cys Trp Met Gly Leu Gly Cys Trp Leu Ser Leu
1 5 10 15

Ser Gly Leu Ser Gly Val Val Arg Ala Ser Pro Arg Ser Pro Arg Pro
20 25 30

Arg Arg Gly Ala Ala Cys Gly Glu Thr Leu Met Pro Xaa
35 40 45

<210> 134
<211> 197
<212> PRT
<213> Homo sapiens

<400> 134
Met Ala Gly Pro Trp Thr Phe Thr Leu Leu Cys Gly Leu Leu Ala Ala
1 5 10 15

Thr Leu Ile Gln Ala Thr Leu Ser Pro Thr Ala Val Leu Ile Leu Gly
20 25 30

Pro Lys Val Ile Lys Glu Lys Leu Thr Gln Glu Leu Lys Asp His Asn
35 40 45

Ala Thr Ser Ile Leu Gln Gln Leu Pro Leu Leu Ser Ala Met Arg Glu

50 55 60

Lys Pro Ala Gly Gly Ile Pro Val Leu Gly Ser Leu Val Asn Thr Val
65 70 75 80

Leu Lys His Ile Ile Trp Leu Lys Val Ile Thr Ala Asn Ile Leu Gln
85 90 95

Leu Gln Val Lys Pro Ser Ala Asn Asp Gln Glu Leu Leu Val Lys Ile
100 105 110

Pro Leu Asp Met Val Ala Gly Phe Asn Thr Pro Leu Val Lys Thr Ile
115 120 125

Val Glu Phe His Met Thr Thr Glu Ala Gln Ala Thr Ile Arg Met Asp
130 135 140

Thr Ser Ala Ser Gly Pro Thr Arg Leu Val Leu Ser Asp Cys Ala Thr
145 150 155 160

Ser His Gly Ser Leu Arg Ile Gln Leu Leu His Lys Leu Ser Phe Leu
165 170 175

Val Asn Ala Leu Ala Lys Gln Val Met Asn Leu Leu Val Pro Ser Met
180 185 190

Pro Arg Trp Pro Asn
195

<210> 135
<211> 46
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (11)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (46)
<223> Xaa equals stop translation

<400> 135
Met His Arg Gln Leu Leu Gly Phe Cys Phe Xaa Phe Cys Phe Phe Phe
1 5 10 15

Lys Arg His Cys Asp Cys Ile Leu Leu Tyr Leu Ile Gly Phe Val Phe
20 25 30

Leu Leu Thr Met Val Lys Ile His Leu Ser Glu His Ser Xaa
35 40 45

<210> 136
<211> 41
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (41)
<223> Xaa equals stop translation

<400> 136
Met Leu Lys Arg Val Ile Leu Leu Val Glu Met Phe Ile His Phe Leu
1 5 10 15

Ile Tyr Ala Lys Ser Phe Tyr His Lys Ser Trp Glu Gln Leu Ser Phe
20 25 30

Thr His Tyr Leu Leu Gln Ile Ser Xaa
35 40

<210> 137
<211> 85
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (48)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (85)
<223> Xaa equals stop translation

<400> 137
Met Pro Ile Leu Val Phe Ser Ile Cys Leu Gln Cys Thr Leu Phe Arg
1 5 10 15

Ser Glu Ala Ile Ile Phe Gln Glu Glu Arg Asn His Gln Val Thr Leu
20 25 30

Leu Lys Ala Val Lys Thr Lys Phe Gln Ser Gly Thr Gly Leu Arg Xaa
35 40 45

Pro Val Leu Glu Tyr Ala Lys Ser Ile Gln Ile Ile Ser Lys Tyr Thr
50 55 60

Cys Gly Thr Val Leu Pro Val Phe Lys Met Arg Arg Tyr Tyr Val Gly
65 70 75 80

Gln Lys Cys Gln Xaa
85

<210> 138
<211> 201
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (144)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (149)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (160)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (173)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (177)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (189)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (201)
<223> Xaa equals stop translation

<400> 138
Met Phe Phe Leu Leu Cys Leu Val Ala Leu Glu Ile Lys Gly Phe Thr
1 5 10 15

Phe Ser Ala Arg Gly Ala Arg Asp Arg Phe Leu Asn Lys Ser Gly Pro
20 25 30

Gln Pro Gly Lys Lys Met Lys Thr Thr His Cys Lys Gln Pro Leu Phe
35 40 45

Ser Lys Pro Gly Gln Val Arg Gly Ala Leu Arg Lys Ala Arg Gly Arg
50 55 60

Gln Glu Glu Arg Glu Ala Val Gly Met Trp Gly Gly Arg Gly His Ser
65 70 75 80

Tyr Pro Glu Tyr Ile Lys Thr Ser Glu Val Thr Glu Val Arg Asp Ser
85 90 95

Pro Lys His Pro Gln Val Gln Pro Phe Leu Thr Thr Arg Val Thr Cys
100 105 110

Arg Val Pro Gly His Leu Gln Val Leu Glu Ala Leu Cys Gly Ala Trp
115 120 125

Gly Ser Met Phe Lys His Ala Leu Val Val Val Gln Val Pro Arg Xaa
130 135 140

Arg Gly Arg Ala Xaa Leu Gly Ser Glu Trp Gln Val Gly Gln Leu Xaa

145 150 155 160

Leu Ile Leu Leu His Gly Thr Gln His Trp Ala Ala Xaa Leu Val Pro
165 170 175

Xaa Leu Pro Gln Glu Ser Ile Leu Pro Ala Gln Ser Xaa Arg Val Thr
180 185 190

Asn Thr Pro Gly Thr Glu Glu Thr Xaa
195 200

<210> 139
<211> 325
<212> PRT
<213> Homo sapiens

<400> 139
Met Gly Ser Gln Val Ser Ser Met Leu Lys Leu Ala Leu Gln Asn Cys
1 5 10 15

Cys Pro Gln Leu Trp Gln Arg His Ser Ala Arg Asp Arg Gln Cys Ala
20 25 30

Arg Val Leu Ala Asp Glu Arg Ser Pro Gln Pro Gly Ala Ser Pro Gln
35 40 45

Glu Asp Ile Ala Asn Phe Gln Val Leu Val Lys Ile Leu Pro Val Met
50 55 60

Val Thr Leu Val Pro Tyr Trp Met Val Tyr Phe Gln Met Gln Ser Thr
65 70 75 80

Tyr Val Leu Gln Gly Leu His Leu His Ile Pro Asn Ile Phe Pro Ala
85 90 95

Asn Pro Ala Asn Ile Ser Val Ala Leu Arg Ala Gln Gly Ser Ser Tyr
100 105 110

Thr Ile Pro Glu Ala Trp Leu Leu Leu Ala Asn Val Val Val Val Leu
115 120 125

Ile Leu Val Pro Leu Lys Asp Arg Leu Ile Asp Pro Leu Leu Leu Arg
130 135 140

Cys Lys Leu Leu Pro Ser Ala Leu Gln Lys Met Ala Leu Gly Met Phe
145 150 155 160

Phe Gly Phe Thr Ser Val Ile Val Ala Gly Val Leu Glu Met Glu Arg
165 170 175

Leu His Tyr Ile His His Asn Glu Thr Val Ser Gln Gln Ile Gly Glu
180 185 190

Val Leu Tyr Asn Ala Ala Pro Leu Ser Ile Trp Trp Gln Ile Pro Gln
195 200 205

Tyr Leu Leu Ile Gly Ile Ser Glu Ile Phe Ala Ser Ile Pro Gly Leu
210 215 220

Glu Phe Ala Tyr Ser Glu Ala Pro Arg Ser Met Gln Gly Ala Ile Met
225 230 235 240

Gly Ile Phe Phe Cys Leu Ser Gly Val Gly Ser Leu Leu Gly Ser Ser
245 250 255

Leu Val Ala Leu Leu Ser Leu Pro Gly Gly Trp Leu His Cys Pro Lys
260 265 270

Asp Phe Gly Asn Ile Asn Asn Cys Arg Met Asp Leu Tyr Phe Phe Leu
275 280 285

Leu Ala Gly Ile Gln Ala Val Thr Ala Leu Leu Phe Val Trp Ile Ala
290 295 300

Gly Arg Tyr Glu Arg Ala Ser Gln Gly Pro Ala Ser His Ser Arg Phe
305 310 315 320

Ser Arg Asp Arg Gly
325

<210> 140
<211> 119
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (107)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (119)
<223> Xaa equals stop translation

<400> 140
Met Val Phe Val His Leu Tyr Leu Gly Asn Val Leu Ala Leu Leu Leu
1 5 10 15

Phe Val His Tyr Ser Asn Gly Asp Glu Ser Ser Asp Pro Gly Pro Gln
20 25 30

His Arg Ala Gln Gly Pro Gly Pro Glu Pro Thr Leu Gly Pro Leu Thr
35 40 45

Arg Leu Glu Gly Ile Lys Val Gly His Glu Arg Lys Val Gln Leu Val
50 55 60

Thr Asp Arg Asp His Phe Ile Arg Thr Leu Ser Leu Lys Pro Leu Leu
65 70 75 80

Phe Glu Ile Pro Gly Phe Leu Thr Asp Glu Glu Cys Arg Leu Ile Ile
85 90 95

His Leu Ala Gln Met Lys Gly Leu Gln Arg Xaa Arg Ser Cys Leu Leu
100 105 110

Lys Ser Met Lys Arg Gln Xaa

115

<210> 141
<211> 48
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (8)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (19)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (48)
<223> Xaa equals stop translation

<400> 141
Met Lys Leu Thr Ile Phe Phe Xaa Phe Pro Gln Thr Ile Thr Gly Leu
1 5 10 15

Leu Gln Xaa Leu Met Ser Arg Gln Val Glu Asp Val Ala Phe Leu Pro
20 25 30

Leu Pro His Pro Val Phe Ser Phe Ser Phe Phe Phe Pro Leu Val Xaa
35 40 45

<210> 142
<211> 520
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (205)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (207)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (213)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (225)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (520)
<223> Xaa equals stop translation

<400> 142
Met Gln Gly Gly Gln Arg Pro His Leu Leu Leu Leu Leu Ala Val
1 5 10 15

Cys Leu Gly Ala Gln Ser Arg Asn Gln Glu Glu Arg Leu Leu Ala Asp
20 25 30

Leu Met Arg Asn Tyr Asp Pro His Leu Arg Pro Ala Glu Arg Asp Ser
35 40 45

Asp Val Val Asn Val Ser Leu Lys Leu Thr Leu Thr Asn Leu Ile Ser
50 55 60

Leu Asn Glu Arg Glu Glu Ala Leu Thr Thr Asn Val Trp Ile Glu Met
65 70 75 80

Gln Trp Cys Asp Tyr Arg Leu Arg Trp Asp Pro Lys Asp Tyr Glu Gly
85 90 95

Leu Trp Ile Leu Arg Val Pro Ser Thr Met Val Trp Arg Pro Asp Ile
100 105 110

Val Leu Glu Asn Asn Val Asp Gly Val Phe Glu Val Ala Leu Tyr Cys
115 120 125

Asn Val Leu Val Ser Pro Asp Gly Cys Ile Tyr Trp Leu Pro Pro Ala
130 135 140

Ile Phe Arg Ser Ser Cys Ser Ile Ser Val Thr Tyr Phe Pro Phe Asp
145 150 155 160

Trp Gln Asn Cys Ser Leu Ile Phe Gln Ser Gln Thr Tyr Ser Thr Ser
165 170 175

Glu Ile Asn Leu Gln Leu Ser Gln Glu Asp Gly Gln Ala Ile Glu Trp
180 185 190

Ile Phe Ile Asp Pro Glu Ala Phe Thr Glu Asn Gly Xaa Trp Xaa Ile
195 200 205

Arg His Arg Pro Xaa Lys Met Leu Leu Asp Ser Val Ala Pro Ala Glu
210 215 220

Xaa Ala Gly His Gln Lys Val Val Phe Tyr Leu Leu Ile Gln Arg Lys
225 230 235 240

Pro Leu Phe Tyr Val Ile Asn Ile Ile Ala Pro Cys Val Leu Ile Ser
245 250 255

Ser Val Ala Ile Leu Ile Tyr Phe Leu Pro Ala Lys Ala Gly Gly Gln
260 265 270

Lys Cys Thr Val Ala Thr Asn Val Leu Leu Ala Gln Thr Val Phe Leu

275 280 285

Phe Leu Val Ala Lys Lys Val Pro Glu Thr Ser Gln Ala Val Pro Leu
290 295 300

Ile Ser Lys Tyr Leu Thr Phe Leu Met Val Val Thr Ile Leu Ile Val
305 310 315 320

Val Asn Ser Val Val Val Leu Asn Val Ser Leu Arg Ser Pro His Thr
325 330 335

His Ser Met Ala Arg Gly Val Arg Lys Val Phe Leu Arg Leu Leu Pro
340 345 350

Gln Leu Leu Arg Met His Val Arg Pro Leu Ala Pro Ala Ala Val Gln
355 360 365

Asp Ala Arg Phe Arg Leu Gln Asn Gly Ser Ser Ser Gly Trp Pro Ile
370 375 380

Met Ala Arg Glu Glu Gly Asp Leu Cys Leu Pro Arg Ser Glu Leu Leu
385 390 395 400

Phe Arg Gln Arg Gln Arg Asn Gly Leu Val Gln Ala Val Leu Glu Lys
405 410 415

Leu Glu Asn Gly Pro Glu Val Arg Gln Ser Gln Glu Phe Cys Gly Ser
420 425 430

Leu Lys Gln Ala Ser Pro Ala Ile Gln Ala Cys Val Asp Ala Cys Asn
435 440 445

Leu Met Ala Arg Ala Arg Arg Gln Gln Ser His Phe Asp Ser Gly Asn
450 455 460

Glu Glu Trp Leu Leu Val Gly Arg Val Leu Asp Arg Val Cys Phe Leu
465 470 475 480

Ala Met Leu Ser Leu Phe Ile Cys Gly Thr Ala Gly Ile Phe Leu Met
485 490 495

Ala His Tyr Asn Gln Val Pro Asp Leu Pro Phe Pro Gly Asp Pro Arg
500 505 510

Pro Tyr Leu Pro Leu Pro Asp Xaa
515 520

<210> 143
<211> 48
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (48)
<223> Xaa equals stop translation

<400> 143
Met Leu Leu Phe Ser Ser Arg Phe Ile Met Phe Leu Trp Pro Pro Val

86

1 5 10 15

Ser Gly Val Cys Leu Ser Phe Ile Arg Asp Arg Ser Phe Leu Pro Met
20 25 30

Cys His Phe Ile Tyr Val Leu Ile Leu Cys Asn Ser Ile Ala Leu Xaa
35 40 45

<210> 144
<211> 431
<212> PRT
<213> Homo sapiens

<400> 144
Met Ser Trp Val Gln Ala Thr Leu Leu Ala Arg Gly Leu Cys Arg Ala
1 5 10 15

Trp Gly Gly Thr Cys Gly Ala Ala Leu Thr Gly Thr Ser Ile Ser Gln
20 25 30

Val Pro Arg Arg Leu Pro Arg Gly Leu His Cys Ser Ala Ala Ala His
35 40 45

Ser Ser Glu Gln Ser Leu Val Pro Ser Pro Pro Glu Pro Arg Gln Arg
50 55 60

Pro Thr Lys Ala Leu Val Pro Phe Glu Asp Leu Phe Gly Gln Ala Pro
65 70 75 80

Gly Gly Glu Arg Asp Lys Ala Ser Phe Leu Gln Thr Val Gln Lys Phe
85 90 95

Ala Glu His Ser Val Arg Lys Arg Gly His Ile Asp Phe Ile Tyr Leu
100 105 110

Ala Leu Arg Lys Met Arg Glu Tyr Gly Val Glu Arg Asp Leu Ala Val
115 120 125

Tyr Asn Gln Leu Leu Asn Ile Phe Pro Lys Glu Val Phe Arg Pro Arg
130 135 140

Asn Ile Ile Gln Arg Ile Phe Val His Tyr Pro Arg Gln Gln Glu Cys
145 150 155 160

Gly Ile Ala Val Leu Glu Gln Met Glu Asn His Gly Val Met Pro Asn
165 170 175

Lys Glu Thr Glu Phe Leu Leu Ile Gln Ile Phe Gly Arg Lys Ser Tyr
180 185 190

Pro Met Leu Lys Leu Val Arg Leu Lys Leu Trp Phe Pro Arg Phe Met
195 200 205

Asn Val Asn Pro Phe Pro Val Pro Arg Asp Leu Pro Gln Asp Pro Val
210 215 220

```
Glu Leu Ala Met Phe Gly Leu Arg His Met Glu Pro Asp Leu Ser Ala
225                 230                 235                 240

Arg Val Thr Ile Tyr Gln Val Pro Leu Pro Lys Asp Ser Thr Gly Ala
                245                 250                 255

Ala Asp Pro Pro Gln Pro His Ile Val Gly Ile Gln Ser Pro Asp Gln
            260                 265                 270

Gln Ala Ala Leu Ala Arg His Asn Pro Ala Arg Pro Val Phe Val Glu
        275                 280                 285

Gly Pro Phe Ser Leu Trp Leu Arg Asn Lys Cys Val Tyr Tyr His Ile
    290                 295                 300

Leu Arg Ala Asp Leu Leu Pro Pro Glu Glu Arg Glu Val Glu Glu Thr
305                 310                 315                 320

Pro Glu Glu Trp Asn Leu Tyr Tyr Pro Met Gln Leu Asp Leu Glu Tyr
                325                 330                 335

Val Arg Ser Gly Trp Asp Asn Tyr Glu Phe Asp Ile Asn Glu Val Glu
            340                 345                 350

Glu Gly Pro Val Phe Ala Met Cys Met Ala Gly Ala His Asp Gln Ala
        355                 360                 365

Thr Met Ala Lys Trp Ile Gln Gly Leu Gln Glu Thr Asn Pro Thr Leu
    370                 375                 380

Ala Gln Ile Pro Val Val Phe Arg Leu Ala Gly Ser Thr Arg Glu Leu
385                 390                 395                 400

Gln Thr Ser Ser Ala Gly Leu Glu Glu Pro Pro Leu Pro Glu Asp His
                405                 410                 415

Gln Glu Glu Asp Asp Asn Leu Gln Arg Gln Gln Gln Gly Gln Ser
            420                 425                 430

<210> 145
<211> 443
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (364)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (443)
<223> Xaa equals stop translation

<400> 145
Met Trp Phe Thr Tyr Leu Leu Leu Tyr Leu His Ser Val Arg Ala Tyr
  1               5                  10                  15

Ser Ser Arg Gly Ala Gly Cys Cys Cys Cys Trp Ala Arg Trp Arg Arg
```

```
                20                  25                  30

Ala Val His Thr Ala Arg Gly Leu Arg Gly Arg Pro Arg Arg Gln Leu
        35                  40                  45

Leu Arg Pro Leu Arg Pro Ala Gln Gly Leu Ala Pro Gly Arg His Arg
    50                  55                  60

Leu Arg Pro Ala Val Leu Pro Leu His Leu Gln Pro Leu Pro Gly Leu
65                  70                  75                  80

Trp Gly Gly His Ala Glu Trp Ala Ala Leu Leu Tyr Tyr Gly Pro Phe
                85                  90                  95

Ile Val Ile Phe Gln Phe Gly Trp Ala Ser Thr Gln Ile Ser His Leu
            100                 105                 110

Ser Leu Ile Pro Glu Leu Val Thr Asn Asp His Glu Lys Val Glu Leu
        115                 120                 125

Thr Ala Leu Arg Tyr Ala Phe Thr Val Val Ala Asn Ile Thr Val Tyr
    130                 135                 140

Gly Ala Ala Trp Leu Leu Leu His Leu Gln Gly Ser Ser Arg Val Glu
145                 150                 155                 160

Pro Thr Gln Asp Ile Ser Ile Ser Asp Gln Leu Gly Gly Gln Asp Val
                165                 170                 175

Pro Val Phe Arg Asn Leu Ser Leu Leu Val Val Gly Val Gly Ala Val
            180                 185                 190

Phe Ser Leu Leu Phe His Leu Gly Thr Arg Glu Arg Arg Arg Pro His
        195                 200                 205

Ala Glu Glu Pro Gly Glu His Thr Pro Leu Leu Ala Pro Ala Thr Ala
    210                 215                 220

Gln Pro Leu Leu Leu Trp Lys His Trp Leu Arg Glu Pro Ala Phe Tyr
225                 230                 235                 240

Gln Val Gly Ile Leu Tyr Met Thr Thr Arg Leu Ile Val Asn Leu Ser
                245                 250                 255

Gln Thr Tyr Met Ala Met Tyr Leu Thr Tyr Ser Leu His Leu Pro Lys
            260                 265                 270

Lys Phe Ile Ala Thr Ile Pro Leu Val Met Tyr Leu Ser Gly Phe Leu
        275                 280                 285

Ser Ser Phe Leu Met Lys Pro Ile Asn Lys Cys Ile Gly Arg Asn Met
    290                 295                 300

Thr Tyr Phe Ser Gly Leu Leu Val Ile Leu Ala Phe Ala Ala Trp Val
305                 310                 315                 320

Ala Leu Ala Glu Gly Leu Gly Val Ala Val Tyr Ala Ala Ala Val Leu
                325                 330                 335
```

```
Leu Gly Ala Gly Cys Ala Thr Ile Leu Val Thr Ser Leu Ala Met Thr
            340                 345                 350

Ala Asp Leu Ile Gly Pro His Thr Asn Ser Gly Xaa Phe Val Tyr Gly
        355                 360                 365

Ser Met Ser Phe Leu Asp Lys Val Ala Asn Gly Leu Ala Val Met Ala
    370                 375                 380

Ile Gln Ser Leu His Pro Cys Pro Ser Glu Leu Cys Cys Arg Ala Cys
385                 390                 395                 400

Val Ser Phe Tyr His Trp Ala Met Val Ala Val Thr Gly Gly Val Gly
                405                 410                 415

Val Ala Ala Ala Leu Cys Leu Cys Ser Leu Leu Leu Trp Pro Thr Arg
            420                 425                 430

Leu Arg Arg Trp Asp Arg Asp Ala Arg Pro Xaa
        435                 440
```

<210> 146
<211> 76
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (76)
<223> Xaa equals stop translation

<400> 146

```
Met Ser Arg Phe Ile Leu Asn His Leu Val Leu Ala Ile Pro Leu Arg
  1               5                  10                  15

Val Leu Val Val Leu Trp Ala Phe Val Leu Gly Leu Ser Arg Val Met
             20                  25                  30

Leu Gly Arg His Asn Val Thr Asp Val Ala Phe Gly Phe Phe Leu Gly
         35                  40                  45

Tyr Met Gln Tyr Ser Ile Val Asp Tyr Cys Trp Leu Ser Pro His Asn
     50                  55                  60

Ala Pro Val Leu Phe Leu Leu Trp Ser Gln Arg Xaa
 65                  70                  75
```

<210> 147
<211> 52
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (52)
<223> Xaa equals stop translation

<400> 147

```
Met Ala Gly Trp Phe Arg Gly Phe Phe Gly Phe Leu Phe Phe Phe Leu
```

90
1 5 10 15

Cys Leu Phe Asn Leu Lys Leu Phe Lys Leu Lys His Ser Gln Met Phe
20 25 30

Gly Gly Lys His Pro Leu Lys Met Gly Pro Cys Ala Cys Leu Leu Gly
35 40 45

Arg Arg Ser Xaa
50

<210> 148
<211> 209
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (3)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (39)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 148
Met Ala Xaa Ser Ser Arg Gly Asn Ala Asp Ser Ile Val Ala Ser Leu
1 5 10 15

Val Leu Met Val Leu Tyr Leu Ile Lys Lys Arg Leu Val Ala Cys Ala
20 25 30

Ala Val Phe Tyr Gly Phe Xaa Val His Met Lys Ile Tyr Pro Val Thr
35 40 45

Tyr Ile Leu Pro Ile Thr Leu His Leu Leu Pro Asp Arg Asp Asn Asp
50 55 60

Lys Ser Leu Arg Gln Phe Arg Tyr Thr Phe Gln Ala Cys Leu Tyr Glu
65 70 75 80

Leu Leu Lys Lys Leu Cys Asn Arg Ala Val Leu Leu Phe Val Ala Val
85 90 95

Ala Gly Leu Thr Phe Phe Ala Leu Ser Phe Gly Phe Tyr Tyr Glu Tyr
100 105 110

Gly Trp Glu Phe Leu Glu His Thr Tyr Phe Tyr His Leu Thr Arg Arg
115 120 125

Asp Ile Arg His Asn Phe Ser Pro Tyr Phe Tyr Met Leu Tyr Leu Thr
130 135 140

Ala Glu Ser Lys Trp Ser Phe Ser Leu Gly Ile Ala Ala Phe Leu Pro
145 150 155 160

Gln Leu Ile Leu Leu Ser Ala Val Ser Phe Ala Tyr Tyr Arg Asp Leu
165 170 175

Val Phe Cys Cys Phe Leu His Thr Ser Ile Phe Val Thr Phe Asn Lys
180 185 190

Val Cys Thr Ser Gln Tyr Phe Leu Trp Val Pro Leu Ala Tyr Cys Leu
195 200 205

Leu

<210> 149
<211> 219
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (168)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (174)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (198)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (213)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (219)
<223> Xaa equals stop translation

<400> 149
Met Arg Ala Leu Leu Ala Leu Cys Leu Leu Leu Gly Trp Leu Arg Trp
1 5 10 15

Gly Pro Ala Gly Ala Gln Gln Ser Gly Glu Tyr Cys His Gly Trp Val
20 25 30

Asp Val Gln Gly Asn Tyr His Glu Gly Phe Gln Cys Pro Glu Asp Phe
35 40 45

Asp Thr Leu Asp Ala Thr Ile Cys Cys Gly Ser Cys Ala Leu Arg Tyr
50 55 60

Cys Cys Ala Ala Ala Asp Ala Arg Leu Glu Gln Gly Gly Cys Thr Asn
65 70 75 80

Asp Arg Arg Glu Leu Glu His Pro Gly Ile Thr Ala Gln Pro Val Tyr
85 90 95

Val Pro Phe Leu Ile Val Gly Ser Ile Phe Ile Ala Phe Ile Ile Leu
100 105 110

Gly Ser Val Val Ala Ile Tyr Cys Cys Thr Cys Leu Arg Pro Lys Glu
115 120 125

Pro Ser Gln Gln Pro Ile Arg Phe Ser Leu Arg Ser Tyr Gln Thr Glu
130 135 140

Thr Leu Pro Met Ile Leu Thr Ser Thr Ser Pro Arg Ala Pro Ser Arg
145 150 155 160

Gln Ser Ser Thr Ala Thr Ser Xaa Ser Phe Thr Gly Gly Xaa Ile Arg
165 170 175

Arg Phe Phe Ser Ala Ile Trp Phe Pro Gly Val Thr Pro Val Phe Arg
180 185 190

Leu Pro Pro Ser Ala Xaa Ala Pro Thr Gly Trp Glu Glu Leu Ser Arg
195 200 205

Leu Ser Val Pro Xaa Asp Thr Pro Arg Pro Xaa
210 215

<210> 150
<211> 50
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (41)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (50)
<223> Xaa equals stop translation

<400> 150
Met Gly Ala His Ser Phe Gly Phe Gln Leu Phe Met Ser Val Ser Val
1 5 10 15

Leu Trp Gly Arg Leu Cys Leu Tyr Gly Arg Phe Ser Val Ile Thr Phe
20 25 30

Ala Ser Pro Pro Thr Thr Phe Met Xaa Ile Gln Cys Cys Ser His Cys
35 40 45

Ser Xaa
50

<210> 151
<211> 41
<212> PRT
<213> Homo sapiens

<220>
<221> SITE

<222> (41)
<223> Xaa equals stop translation

<400> 151
Met His Ile His Leu Asp Thr Ser Ser Leu Lys Thr Leu His Leu Gly
1 5 10 15

Thr Leu Phe Phe Leu Phe Tyr Leu Ala Leu Thr Gln Asn Glu Glu Asn
20 25 30

Ile Cys Asp Gly Lys Val Thr Leu Xaa
35 40

<210> 152
<211> 108
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (108)
<223> Xaa equals stop translation

<400> 152
Met Pro Ile Ile Val Leu Ile Leu Val Ser Leu Leu Ser Gln Leu Met
1 5 10 15

Val Ser Asn Pro Pro Tyr Ser Leu Tyr Pro Arg Ser Gly Thr Gly Gln
20 25 30

Thr Ile Lys Met Gln Thr Glu Asn Leu Gly Val Val Tyr Tyr Val Asn
35 40 45

Lys Asp Phe Lys Asn Glu Tyr Lys Gly Met Leu Leu Gln Lys Val Glu
50 55 60

Lys Ser Val Glu Glu Asp Tyr Val Thr Asn Ile Arg Asn Asn Cys Trp
65 70 75 80

Lys Glu Arg Gln Gln Lys Thr Asp Met Gln Tyr Ala Ala Lys Val Tyr
85 90 95

Arg Asp Asp Arg Leu Arg Arg Arg Gln Met Pro Xaa
100 105

<210> 153
<211> 157
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (157)
<223> Xaa equals stop translation

<400> 153
Met Gln Ala Ser Leu Trp Glu Pro Pro Arg Ser Gly Leu Pro Leu Trp
1 5 10 15

Ala Glu Gly Leu Thr Phe Phe Tyr Cys Tyr Met Leu Leu Leu Val Leu
20 25 30

Pro Cys Val Ala Leu Ser Glu Val Ser Met Gln Gly Glu His Ile Ala
35 40 45

Pro Gln Lys Met Met Leu Tyr Pro Val Leu Ser Leu Ala Thr Val Asn
50 55 60

Val Val Ala Val Leu Ala Arg Ala Ala Asn Met Ala Leu Phe Arg Asp
65 70 75 80

Ser Arg Val Ser Ala Ile Phe Val Gly Lys Asn Val Val Ala Leu Ala
85 90 95

Thr Lys Ala Cys Thr Phe Leu Glu Tyr Arg Arg Gln Val Arg Asp Phe
100 105 110

Pro Pro Pro Ala Leu Ser Leu Glu Leu Gln Pro Pro Pro Pro Gln Arg
115 120 125

Asn Ser Val Pro Pro Pro Pro Pro Leu His Gly Pro Pro Gly Arg Pro
130 135 140

His Met Ser Ser Pro Thr Arg Asp Pro Leu Asp Thr Xaa
145 150 155

<210> 154
<211> 151
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (151)
<223> Xaa equals stop translation

<400> 154
Met Gly Tyr Leu Phe Phe Leu Leu Phe Met Ile Cys Trp Met Ile Tyr
1 5 10 15

Gly Cys Ile Ser Tyr Trp Gly Leu His Cys Glu Thr Thr Tyr Thr Lys
20 25 30

Asp Gly Phe Trp Thr Tyr Ile Thr Gln Ile Ala Thr Cys Ser Pro Trp
35 40 45

Met Phe Trp Met Phe Leu Asn Ser Val Phe His Phe Met Trp Val Ala
50 55 60

Val Leu Leu Met Cys Gln Met Tyr Gln Ile Ser Cys Leu Gly Ile Thr
65 70 75 80

Thr Asn Glu Arg Met Asn Ala Arg Arg Tyr Lys His Phe Lys Val Thr
85 90 95

Thr Thr Ser Ile Glu Ser Pro Phe Asn His Gly Cys Val Arg Asn Ile
100 105 110

95

Ile Asp Phe Phe Glu Phe Arg Cys Cys Gly Leu Phe Arg Pro Val Ile
115 120 125

Val Asp Trp Thr Arg Gln Tyr Thr Ile Glu Tyr Asp Gln Ile Ser Gly
130 135 140

Ser Gly Tyr Gln Leu Val Xaa
145 150

<210> 155
<211> 71
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (71)
<223> Xaa equals stop translation

<400> 155
Met Ala Leu Thr Leu Leu Leu Ile Gln Ile Ile Phe Leu Ala Leu Gly
1 5 10 15

Lys Ile Ser Phe Ile Phe Val Cys Cys Lys Asp Gly Phe Ala Arg Ile
20 25 30

Ser His Asp Gln Asp Lys Leu Pro Ile Gln Lys Pro Thr Asp Thr Asn
35 40 45

Tyr Ile Met Arg Lys Lys Cys Ile Gln Leu Gly His Ile Ser Phe Glu
50 55 60

Leu Phe Gly Leu Lys Ala Xaa
65 70

<210> 156
<211> 490
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (134)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (389)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 156
Met Leu Ala Leu Thr Phe Met Phe Met Val Leu Glu Val Val Val Ser
1 5 10 15

Arg Val Thr Ser Ser Leu Ala Met Leu Ser Asp Ser Phe His Met Leu
20 25 30

Ser Asp Val Leu Ala Leu Val Val Ala Leu Val Ala Glu Arg Phe Ala
35 40 45

```
Arg Arg Thr His Ala Thr Gln Lys Asn Thr Phe Gly Trp Ile Arg Ala
     50                  55                  60

Glu Val Met Gly Ala Leu Val Asn Ala Ile Phe Leu Thr Gly Leu Cys
 65                  70                  75                  80

Phe Ala Ile Leu Leu Glu Ala Ile Glu Arg Phe Ile Glu Pro His Glu
                 85                  90                  95

Met Gln Gln Pro Leu Val Val Leu Gly Val Gly Val Ala Gly Leu Leu
            100                 105                 110

Val Asn Val Leu Gly Leu Cys Leu Phe His His His Ser Gly Phe Ser
        115                 120                 125

Gln Asp Ser Gly His Xaa His Ser His Gly Gly His Gly His Gly His
    130                 135                 140

Gly Leu Pro Lys Gly Pro Arg Val Lys Ser Thr Arg Pro Gly Ser Ser
145                 150                 155                 160

Asp Ile Asn Val Ala Pro Gly Glu Gln Gly Pro Asp Gln Glu Glu Thr
                165                 170                 175

Asn Thr Leu Val Ala Asn Thr Ser Asn Ser Asn Gly Leu Lys Leu Asp
            180                 185                 190

Pro Ala Asp Pro Glu Asn Pro Arg Ser Gly Asp Thr Val Glu Val Gln
        195                 200                 205

Val Asn Gly Asn Leu Val Arg Glu Pro Asp His Met Glu Leu Glu Glu
    210                 215                 220

Asp Arg Ala Gly Gln Leu Asn Met Arg Gly Val Phe Leu His Val Leu
225                 230                 235                 240

Gly Asp Ala Leu Gly Ser Val Ile Val Val Val Asn Ala Leu Val Phe
                245                 250                 255

Tyr Phe Ser Trp Lys Gly Cys Ser Glu Gly Asp Phe Cys Val Asn Pro
            260                 265                 270

Cys Phe Pro Asp Pro Cys Lys Pro Phe Val Glu Ile Ile Asn Ser Thr
        275                 280                 285

His Ala Ser Val Tyr Glu Ala Gly Pro Cys Trp Val Leu Tyr Leu Asp
    290                 295                 300

Pro Thr Leu Cys Val Val Met Val Cys Ile Leu Leu Tyr Thr Thr Tyr
305                 310                 315                 320

Pro Leu Leu Lys Glu Ser Ala Leu Ile Leu Leu Gln Thr Val Pro Lys
                325                 330                 335

Gln Ile Asp Ile Arg Asn Leu Ile Lys Glu Leu Arg Asn Val Glu Gly
            340                 345                 350

Val Glu Glu Val His Glu Leu His Val Trp Gln Leu Ala Gly Ser Arg
```

355 360 365

Ile Ile Ala Thr Ala His Ile Lys Cys Glu Asp Pro Thr Ser Tyr Met
370 375 380

Glu Val Ala Lys Xaa Ile Lys Asp Val Phe His Asn His Gly Ile His
385 390 395 400

Ala Thr Thr Ile Gln Pro Glu Phe Ala Ser Val Gly Ser Lys Ser Ser
405 410 415

Val Val Pro Cys Glu Leu Ala Cys Arg Thr Gln Cys Ala Leu Lys Gln
420 425 430

Cys Cys Gly Thr Leu Pro Gln Ala Pro Ser Gly Lys Asp Ala Glu Lys
435 440 445

Thr Pro Ala Val Ser Ile Ser Cys Leu Glu Leu Ser Asn Asn Leu Glu
450 455 460

Lys Lys Pro Arg Arg Thr Lys Ala Glu Asn Ile Pro Ala Val Val Ile
465 470 475 480

Glu Ile Lys Asn Met Pro Lys Gln Thr Thr
485 490

<210> 157
<211> 31
<212> PRT
<213> Homo sapiens

<400> 157
Met Gln Pro Cys Val Ile Ser Trp Glu Gln Cys Ser Phe Val Ser Pro
1 5 10 15

Arg Gly Pro His Val Tyr Ile Cys Phe His Asp Gln Arg Arg Phe
20 25 30

<210> 158
<211> 115
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (96)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (100)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 158
Met Leu Gly Leu Leu Gly Ser Thr Ala Leu Val Gly Trp Ile Thr Gly
1 5 10 15

Ala Ala Val Ala Val Leu Leu Leu Leu Leu Leu Leu Ala Thr Cys Leu
20 25 30

```
Phe His Gly Arg Gln Asp Cys Asp Val Glu Arg Asn Arg Thr Ala Ala
         35                  40                  45

Gly Gly Asn Arg Val Arg Arg Ala Gln Pro Trp Pro Phe Arg Arg Arg
     50                  55                  60

Gly His Leu Gly Ile Phe His His His Arg His Pro Gly His Val Ser
 65                  70                  75                  80

His Val Pro Asn Val Gly Leu His His His His His Pro Arg His Xaa
                 85                  90                  95

Pro His His Xaa His His His His His Pro His Arg His His Pro Arg
            100                 105                 110

His Ala Arg
        115
```

<210> 159
<211> 380
<212> PRT
<213> Homo sapiens

<400> 159

```
Met Lys Arg Ala Ser Ala Gly Gly Ser Arg Leu Leu Ala Trp Val Leu
  1               5                  10                  15

Trp Leu Gln Ala Trp Gln Val Ala Ala Pro Cys Pro Gly Ala Cys Val
             20                  25                  30

Cys Tyr Asn Glu Pro Lys Val Thr Thr Ser Cys Pro Gln Gln Gly Leu
         35                  40                  45

Gln Ala Val Pro Val Gly Ile Pro Ala Ala Ser Gln Arg Ile Phe Leu
     50                  55                  60

His Gly Asn Arg Ile Ser His Val Pro Ala Ala Ser Phe Arg Ala Cys
 65                  70                  75                  80

Arg Asn Leu Thr Ile Leu Trp Leu His Ser Asn Val Leu Ala Arg Ile
                 85                  90                  95

Asp Ala Ala Ala Phe Thr Gly Leu Ala Leu Leu Glu Gln Leu Asp Leu
            100                 105                 110

Ser Asp Asn Ala Gln Leu Arg Ser Val Asp Pro Ala Thr Phe His Gly
        115                 120                 125

Leu Gly Arg Leu His Thr Val His Leu Asp Arg Cys Gly Leu Gln Glu
    130                 135                 140

Leu Gly Pro Gly Leu Phe Arg Gly Leu Ala Ala Leu Gln Tyr Leu Tyr
145                 150                 155                 160

Leu Gln Asp Asn Ala Leu Gln Ala Leu Pro Asp Asp Thr Phe Arg Asp
                165                 170                 175

Leu Gly Asn Leu Thr His Leu Phe Leu His Gly Asn Arg Ile Ser Ser
```

180 185 190

Val Pro Glu Arg Ala Phe Arg Gly Leu His Ser Leu Asp Arg Leu Leu
195 200 205

Leu His Gln Asn Arg Val Ala His Val His Pro His Ala Phe Arg Asp
210 215 220

Leu Gly Arg Leu Met Thr Leu Tyr Leu Phe Ala Asn Asn Leu Ser Ala
225 230 235 240

Leu Pro Thr Glu Ala Leu Ala Pro Leu Arg Ala Leu Gln Tyr Leu Arg
245 250 255

Leu Asn Asp Asn Pro Trp Val Cys Asp Cys Arg Ala Arg Pro Leu Trp
260 265 270

Ala Trp Leu Gln Lys Phe Arg Gly Ser Ser Ser Glu Val Pro Cys Ser
275 280 285

Leu Pro Gln Arg Leu Ala Gly Arg Asp Leu Lys Arg Leu Ala Ala Asn
290 295 300

Asp Leu Gln Gly Cys Ala Val Ala Thr Gly Pro Tyr His Pro Ile Trp
305 310 315 320

Thr Gly Arg Ala Thr Asp Glu Glu Pro Leu Gly Leu Pro Lys Cys Cys
325 330 335

Gln Pro Asp Ala Ala Asp Lys Ala Ser Val Leu Glu Pro Gly Arg Pro
340 345 350

Ala Ser Ala Gly Asn Ala Leu Lys Gly Pro Arg Ala Gly Arg Gly Gln
355 360 365

Ala Arg Arg Glu Thr Val Phe Gly Pro Arg Glu His
370 375 380

<210> 160
<211> 92
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (92)
<223> Xaa equals stop translation

<400> 160
Met Arg Leu Cys Val Thr Gly Pro Pro Val Phe Phe Phe Phe Leu Asn
1 5 10 15

Phe Phe Phe Phe Leu Cys Val Gly Ala Cys Leu Gly Asp Leu Lys Ile
20 25 30

Ser Arg Leu Val Tyr Leu Cys Lys Ala Cys Leu Arg Leu Glu Tyr Leu
35 40 45

Gly Lys Glu Ser Asp Ser Met Leu Ser Glu Phe Leu Lys Gly Gln Lys

100

50 55 60

Lys Asn Trp Arg Leu Leu Lys Cys Arg Phe Glu Val Ile Phe Leu Lys
65 70 75 80

Tyr Tyr Phe Gly Phe Cys Asp Ile Val Lys Asn Xaa
85 90

<210> 161
<211> 45
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (45)
<223> Xaa equals stop translation

<400> 161
Met Lys Lys His Thr Lys Cys Gln Trp Leu Lys Met Thr Ile Leu Phe
1 5 10 15

Leu Thr Val Met Lys Ile Gly Tyr Gly Thr Ser Ala Ser Cys Tyr Arg
20 25 30

Pro Glu Val Leu Gly Leu Leu Met Pro His Pro Leu Xaa
35 40 45

<210> 162
<211> 46
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (46)
<223> Xaa equals stop translation

<400> 162
Met Ser Cys Gly Cys Cys Phe Ile His Ile Tyr Asn Leu Leu Leu Ser
1 5 10 15

Leu Cys Tyr Gly Leu Gly Val Glu Arg Val Lys Phe Phe Thr Phe Ser
20 25 30

Ile Leu Lys Lys Glu Thr Met Leu Leu Asn Tyr Leu Phe Xaa
35 40 45

<210> 163
<211> 128
<212> PRT
<213> Homo sapiens

<400> 163
Met Leu Ser Ser Pro Ile Leu Ala Ser Gly Pro Ala Trp Leu Ala Cys
1 5 10 15

Ser Phe Ser His Val Gln Trp Trp Val Cys Leu Ile Ala Gln Val Gln
20 25 30

```
Phe Ser Ala Ala Thr Val Ser Pro Gly Arg Ala Gly Thr Gly Ala Ala
         35                  40                  45

Pro Ser Val Pro Ala Val Trp Ala Ala Glu Ala Arg Gly Pro Ser Val
     50                  55                  60

Pro Ser Thr Leu Gln Gly Ser Pro Val Leu Gln Arg Asp Leu Ala Asn
 65                  70                  75                  80

Pro Pro Pro Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys
                 85                  90                  95

Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys
            100                 105                 110

Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Gly Gly Pro
        115                 120                 125
```

<210> 164
<211> 58
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (58)
<223> Xaa equals stop translation

<400> 164

```
Met His Pro Trp Arg Leu Ser Met Cys Pro Ala Cys Val Leu Ala Ala
  1               5                  10                  15

Leu Pro Ala Leu Cys Ser Cys Leu Cys Ser Pro Asp Ala Arg Pro Pro
             20                  25                  30

His Gly Trp Met Ser Met Pro Phe Thr Pro His Pro Leu Val Ser Arg
         35                  40                  45

Ala Met Pro Thr Cys His Pro Cys Ser Xaa
     50                  55
```

<210> 165
<211> 98
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (98)
<223> Xaa equals stop translation

<400> 165

```
Met Tyr Arg Ala Ile Asp Ser Phe Pro Arg Trp Arg Ser Tyr Phe Tyr
  1               5                  10                  15
```

Phe Ile Thr Leu Ile Phe Phe Leu Ala Trp Leu Val Lys Asn Val Phe
20 25 30

Ile Ala Val Ile Ile Glu Thr Phe Ala Glu Ile Arg Val Gln Phe Gln
35 40 45

Gln Met Trp Gly Ser Arg Ser Ser Thr Thr Ser Thr Ala Thr Thr Gln
50 55 60

Met Phe His Glu Asp Ala Ala Gly Gly Trp Gln Leu Val Ala Val Gly
65 70 75 80

Cys Gln Gln Ala Pro Gly Thr Arg Pro Ser Leu Pro Pro Gly Ala Val
85 90 95

Gln Xaa

<210> 166
<211> 60
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (60)
<223> Xaa equals stop translation

<400> 166
Met Thr Ser Phe Cys Glu Met Leu Lys Gly Ser Ala Ala Gly Cys Leu
1 5 10 15

Val Leu Leu Ala Phe Ala Phe Tyr Leu Ala Cys Ser Phe Ser His Lys
20 25 30

Thr Lys Ser His Ser His Tyr Ala Leu Phe Ile Leu Gln Asp Tyr Leu
35 40 45

Leu Gly Asn Phe Tyr Tyr Ile Pro Leu Ser Pro Xaa
50 55 60

<210> 167
<211> 43
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (43)
<223> Xaa equals stop translation

<400> 167
Met Ser Val Ala His Met His Ala Cys Val Phe Leu Cys Ala Cys Val
1 5 10 15

Phe Cys Leu Ala Glu Asn Ala Leu Glu Ser Val Ile Ile Leu Cys Tyr
20 25 30

Ser Tyr Asn Lys Asp Glu Val Arg Glu His Xaa

35 40

<210> 168
<211> 54
<212> PRT
<213> Homo sapiens

<400> 168
Met Lys Thr His Leu Leu Met Phe Leu Leu Ser Cys Met Ala Arg Cys
1 5 10 15

Thr Gly Ile Val Pro Lys Arg Pro Gln Pro Ala Phe Pro Leu Arg Gly
20 25 30

Arg Arg Arg Lys Asn Ser Phe Leu Phe Leu Leu Ser Phe Ser Ile Glu
35 40 45

Phe Leu Leu Cys Val Trp
50

<210> 169
<211> 53
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (11)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 169
Met Cys Lys Ala Val Cys Lys His Arg Leu Xaa Leu Phe Ala Val Ser
1 5 10 15

Ser Phe Ser Leu Gly Leu Gly Trp Val Cys Val Leu Val Leu Met Leu
20 25 30

Trp Pro Val Arg Leu Ser Leu Ala Pro Arg Pro Val Gln Leu Gln Gln
35 40 45

Arg Arg Ser His Cys
50

<210> 170
<211> 54
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (54)
<223> Xaa equals stop translation

<400> 170
Met Phe Thr Ala Pro Leu Phe Phe Phe Phe Phe Phe Glu Ile Ile Asn
1 5 10 15

Ser Met Arg Asn Leu Gly Leu Asn Ile Cys Leu Leu Cys Leu Leu Ile
20 25 30

Glu His His Ser Arg Pro Ser Val Cys Leu Pro Phe Thr Pro Lys Ile
35 40 45

Leu Thr Lys Lys Phe Xaa
50

<210> 171
<211> 49
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (49)
<223> Xaa equals stop translation

<400> 171
Met Leu Cys Phe Leu Pro Ile Pro Leu Leu Ser Ile Leu Ser Pro Gln
1 5 10 15

Thr Gln Ala Ser Arg Leu Leu Asp Glu Thr Val Arg Arg Lys His Phe
20 25 30

Leu Thr Tyr Pro Phe Gly Ile Ser Ser Ile Ile Thr Gln Ala Leu Leu
35 40 45

Xaa

<210> 172
<211> 224
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (183)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (214)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 172
Met Val Leu Val Ala Leu Ile Leu Leu His Ser Ala Leu Ala Gln Ser
1 5 10 15

Arg Arg Asp Phe Ala Pro Pro Gly Gln Gln Lys Arg Glu Ala Pro Val
20 25 30

Asp Val Leu Thr Gln Ile Gly Arg Ser Val Arg Gly Thr Leu Asp Ala
35 40 45

Trp Ile Gly Pro Glu Thr Met His Leu Val Ser Glu Ser Ser Ser Gln
50 55 60

Val Leu Trp Ala Ile Ser Ser Ala Ile Ser Val Ala Phe Phe Ala Leu

105

65 70 75 80

Ser Gly Ile Ala Ala Gln Leu Leu Asn Ala Leu Gly Leu Ala Gly Asp
85 90 95

Tyr Leu Ala Gln Gly Leu Lys Leu Ser Pro Gly Gln Val Gln Thr Phe
100 105 110

Leu Leu Trp Gly Ala Gly Ala Leu Val Val Tyr Trp Leu Leu Ser Leu
115 120 125

Leu Leu Gly Leu Val Leu Ala Leu Leu Gly Arg Ile Leu Trp Gly Leu
130 135 140

Lys Leu Val Ile Phe Leu Ala Gly Phe Val Ala Leu Met Arg Ser Val
145 150 155 160

Pro Asp Pro Ser Thr Arg Ala Leu Leu Leu Leu Ala Leu Leu Ile Leu
165 170 175

Tyr Ala Leu Leu Ser Arg Xaa Thr Gly Ser Arg Ala Ser Gly Ala Gln
180 185 190

Leu Glu Ala Lys Val Arg Gly Leu Glu Arg Gln Val Glu Glu Leu Arg
195 200 205

Trp Arg Gln Arg Gln Xaa Ala Lys Gly Ala Arg Ser Val Glu Glu Glu
210 215 220

<210> 173
<211> 201
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (10)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (11)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (27)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (50)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE

<222> (60)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (84)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (178)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (180)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (190)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (201)
<223> Xaa equals stop translation

<400> 173

```
Met Leu Gln Arg Met Leu Ile Asp Val Xaa Xaa Phe Leu Phe Leu Phe
  1               5                  10                  15

Ala Val Trp Met Val Ala Phe Gly Val Ala Xaa Gln Gly Ile Leu Arg
             20                  25                  30

Gln Asn Glu Gln Arg Trp Arg Trp Ile Phe Arg Ser Val Ile Tyr Glu
         35                  40                  45

Pro Xaa Leu Ala Met Phe Gly Gln Val Pro Ser Xaa Val Asp Gly Thr
     50                  55                  60

Thr Tyr Asp Phe Ala His Cys Thr Phe Thr Gly Asn Glu Ser Lys Pro
 65                  70                  75                  80

Leu Cys Val Xaa Leu Asp Glu His Asn Leu Pro Arg Phe Pro Glu Trp
                 85                  90                  95

Ile Thr Ile Pro Leu Val Cys Ile Tyr Met Leu Ser Thr Asn Ile Leu
            100                 105                 110

Leu Val Asn Leu Leu Val Ala Met Phe Gly Tyr Thr Val Gly Thr Val
        115                 120                 125

Gln Glu Asn Asn Asp Gln Val Trp Lys Phe Gln Arg Tyr Phe Leu Val
    130                 135                 140

Gln Glu Tyr Cys Ser Arg Leu Asn Ile Pro Phe Pro Phe Ile Val Phe
145                 150                 155                 160
```

Ala Tyr Phe Tyr Met Val Val Lys Lys Cys Phe Lys Cys Cys Cys Lys
165 170 175

Glu Xaa Asn Xaa Glu Ser Ser Val Cys Cys Ser Lys Met Xaa Thr Met
180 185 190

Arg Leu Trp His Gly Arg Val Ser Xaa
195 200

<210> 174
<211> 93
<212> PRT
<213> Homo sapiens

<400> 174
Met Pro Arg Ala Thr Leu Trp Gly His Leu Ser Pro Ala Trp Val Leu
1 5 10 15

Val Pro Trp Thr Pro Arg Ala Cys Gly Gln Ala Ala Pro Gly Arg Gly
20 25 30

His Val Ala Ser Asp His Lys Ser Gly Leu Pro Trp Pro Lys His Cys
35 40 45

Ser Cys Leu His Pro Arg Ala Ser Gln Pro Cys Leu Phe Ser Leu Asn
50 55 60

Ser Asn Arg Thr Val Phe Thr Ala Ile Gln Arg Val Ala Leu Gly Trp
65 70 75 80

Thr Phe Trp Val Gln Ala Asn Leu Val Pro Arg Cys Thr
85 90

<210> 175
<211> 404
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (41)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (77)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (96)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (98)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE
<222> (108)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (122)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (124)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (126)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (175)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (192)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (210)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (236)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (239)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (309)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (335)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (389)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 175

```
Met His Pro Ile Pro Ser Ser Phe Met Ile Lys Ala Val Ser Ser Phe
  1               5                  10                  15

Leu Thr Ala Glu Glu Ala Ser Val Gly Asn Pro Glu Gly Ala Phe Met
             20                  25                  30

Lys Val Leu Gln Ala Arg Lys Asn Xaa Thr Ser Thr Glu Leu Ile Val
         35                  40                  45

Glu Pro Glu Glu Pro Ser Asp Ser Ser Gly Ile Asn Leu Ser Gly Phe
     50                  55                  60

Gly Ser Glu Gln Leu Asp Thr Asn Asp Glu Ser Asp Xaa Ile Ser Thr
 65                  70                  75                  80

Leu Ser Tyr Ile Leu Pro Tyr Phe Ser Ala Val Asn Leu Asp Val Xaa
                 85                  90                  95

Ser Xaa Leu Leu Pro Phe Ile Lys Leu Pro Thr Xaa Gly Asn Ser Leu
            100                 105                 110

Ala Lys Ile Gln Thr Val Gly Gln Asn Xaa Gln Xaa Val Xaa Arg Val
        115                 120                 125

Leu Met Gly Pro Arg Ser Ile Gln Lys Arg His Phe Lys Glu Val Gly
    130                 135                 140

Arg Gln Ser Ile Arg Arg Glu Gln Gly Ala Gln Ala Ser Val Glu Asn
145                 150                 155                 160

Ala Ala Glu Glu Lys Arg Leu Gly Ser Pro Ala Pro Arg Glu Xaa Glu
                165                 170                 175

Gln Pro His Thr Gln Gln Gly Pro Glu Lys Leu Ala Gly Asn Ala Xaa
            180                 185                 190

Tyr Thr Lys Pro Ser Phe Thr Gln Glu His Lys Ala Ala Val Ser Val
        195                 200                 205

Leu Xaa Pro Phe Ser Lys Gly Ala Pro Ser Thr Ser Ser Pro Ala Lys
    210                 215                 220

Ala Leu Pro Gln Val Arg Asp Arg Trp Lys Asp Xaa Thr His Xaa Ile
225                 230                 235                 240

Ser Ile Leu Glu Ser Ala Lys Ala Arg Val Thr Asn Met Lys Ala Ser
                245                 250                 255

Lys Pro Ile Ser His Ser Arg Lys Lys Tyr Arg Phe His Lys Thr Arg
            260                 265                 270

Ser Arg Met Thr His Arg Thr Pro Lys Val Lys Lys Ser Pro Lys Phe
        275                 280                 285

Arg Lys Lys Ser Tyr Leu Ser Arg Leu Met Leu Ala Asn Arg Pro Pro
    290                 295                 300

Phe Ser Ala Ala Xaa Ser Leu Ile Asn Ser Pro Ser Gln Gly Ala Phe
```

110

305 310 315 320

Ser Ser Leu Gly Asp Leu Ser Pro Gln Glu Asn Pro Phe Leu Xaa Val
325 330 335

Ser Ala Pro Ser Glu His Phe Ile Glu Thr Thr Asn Ile Lys Asp Thr
340 345 350

Thr Ala Arg Asn Ala Leu Glu Glu Asn Val Phe Met Glu Asn Thr Asn
355 360 365

Met Pro Glu Val Thr Ile Ser Glu Asn Thr Asn Tyr Asn His Pro Pro
370 375 380

Glu Ala Asp Ser Xaa Gly Thr Ala Phe Asn Leu Gly Pro Thr Val Lys
385 390 395 400

Gln Thr Glu Thr

<210> 176
<211> 387
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (228)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (359)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 176
Met Gly Ala Phe Leu Asp Lys Pro Lys Thr Glu Lys His Asn Ala His
1 5 10 15

Gly Ala Gly Asn Gly Leu Arg Tyr Gly Leu Ser Ser Met Gln Gly Trp
20 25 30

Arg Val Glu Met Glu Asp Ala His Thr Ala Val Val Gly Ile Pro His
35 40 45

Gly Leu Glu Asp Trp Ser Phe Phe Ala Val Tyr Asp Gly His Ala Gly
50 55 60

Ser Arg Val Ala Asn Tyr Cys Ser Thr His Leu Leu Glu His Ile Thr
65 70 75 80

Thr Asn Glu Asp Phe Arg Ala Ala Gly Lys Ser Gly Ser Ala Leu Glu
85 90 95

Leu Ser Val Glu Asn Val Lys Asn Gly Ile Arg Thr Gly Phe Leu Lys
100 105 110

Ile Asp Glu Tyr Met Arg Asn Phe Ser Asp Leu Arg Asn Gly Met Asp
115 120 125

```
Arg Ser Gly Ser Thr Ala Val Gly Val Met Ile Ser Pro Lys His Ile
    130                 135                 140

Tyr Phe Ile Asn Cys Gly Asp Ser Arg Ala Val Leu Tyr Arg Asn Gly
145                 150                 155                 160

Gln Val Cys Phe Ser Thr Gln Asp His Lys Pro Cys Asn Pro Arg Glu
                165                 170                 175

Lys Glu Arg Ile Gln Asn Ala Gly Gly Ser Val Met Ile Gln Arg Val
            180                 185                 190

Asn Gly Ser Leu Ala Val Ser Arg Ala Leu Gly Asp Tyr Asp Tyr Lys
        195                 200                 205

Cys Val Asp Gly Lys Gly Pro Thr Glu Gln Leu Val Ser Pro Glu Pro
    210                 215                 220

Glu Val Tyr Xaa Ile Leu Arg Ala Glu Glu Asp Glu Phe Ile Ile Leu
225                 230                 235                 240

Ala Cys Asp Gly Ile Trp Asp Val Met Ser Asn Glu Glu Leu Cys Glu
                245                 250                 255

Tyr Val Lys Ser Arg Leu Glu Val Ser Asp Asp Leu Glu Asn Val Cys
            260                 265                 270

Asn Trp Val Val Asp Thr Cys Leu His Lys Gly Ser Arg Asp Asn Met
        275                 280                 285

Ser Ile Val Leu Val Cys Phe Ser Asn Ala Pro Lys Val Ser Asp Glu
    290                 295                 300

Ala Val Lys Lys Asp Ser Glu Leu Asp Lys His Leu Glu Ser Arg Val
305                 310                 315                 320

Glu Glu Ile Met Glu Lys Ser Gly Glu Glu Gly Met Pro Asp Leu Ala
                325                 330                 335

His Val Met Arg Ile Leu Ser Ala Glu Asn Ile Pro Asn Leu Pro Pro
            340                 345                 350

Gly Gly Gly Leu Ala Gly Xaa Arg Asn Val Ile Glu Ala Val Tyr Ser
        355                 360                 365

Arg Leu Asn Pro His Arg Glu Ser Asp Gly Gly Ala Gly Asp Leu Glu
    370                 375                 380

Asp Pro Trp
385

<210> 177
<211> 145
<212> PRT
<213> Homo sapiens

<400> 177
Met Ala Phe Phe Thr Gly Leu Trp Gly Pro Phe Thr Cys Val Ser Arg
```

1 5 10 15

Val Leu Ser His His Cys Phe Ser Thr Thr Gly Ser Leu Ser Ala Ile
20 25 30

Gln Lys Met Thr Arg Val Arg Val Val Asp Asn Ser Ala Leu Gly Asn
35 40 45

Ser Pro Tyr His Arg Ala Pro Arg Cys Ile His Val Tyr Lys Lys Asn
50 55 60

Gly Val Gly Lys Val Gly Asp Gln Ile Leu Leu Ala Ile Lys Gly Gln
65 70 75 80

Lys Lys Lys Ala Leu Ile Val Gly His Cys Met Pro Gly Pro Arg Met
85 90 95

Thr Pro Arg Phe Asp Ser Asn Asn Val Val Leu Ile Glu Asp Asn Gly
100 105 110

Asn Pro Val Gly Thr Arg Ile Lys Thr Pro Ile Pro Thr Ser Leu Arg
115 120 125

Lys Arg Glu Gly Glu Tyr Ser Lys Val Leu Ala Ile Ala Gln Asn Phe
130 135 140

Val
145

<210> 178
<211> 140
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (129)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (132)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (134)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 178
Met Phe Phe Ser Leu Pro Gly Leu Trp Gln Ile Ala Ser Phe Thr His
1 5 10 15

Asn Leu Ile Phe His Leu Trp Val Trp Gly Ser Glu Ser Gly Glu His
20 25 30

Leu Gln Ser His Asn Asp Pro Asp Thr Arg Gln Gly Gly His Ile Pro
35 40 45

Ile Arg Leu Leu Gly Glu Ser Ser Ala Ser Val Pro Gly Ser Ser Glu
50 55 60

Gly His Thr Gly Gly Pro Ala Pro Pro Arg Val Gly Gly Ser Ala Gly
65 70 75 80

Ile Ile Arg Thr His Val Val Phe Leu Val Ser Trp Pro Leu Leu Gln
85 90 95

Arg Glu Gln His Arg Leu Ser Trp Lys Leu Pro Ser Val Met Trp Gly
100 105 110

Asp Ser Arg Glu Pro His Leu Ala Arg Leu Asp Gln Ser Lys Trp Pro
115 120 125

Xaa Ala Thr Xaa Ala Xaa Gln Tyr Leu Gly Arg Gly
130 135 140

<210> 179
<211> 127
<212> PRT
<213> Homo sapiens

<400> 179
Met Val Pro Gly Ala Ala Gly Trp Cys Cys Leu Val Leu Trp Leu Pro
1 5 10 15

Ala Cys Val Ala Ala His Gly Phe Arg Ile His Asp Tyr Leu Tyr Phe
20 25 30

Gln Val Leu Ser Pro Gly Asp Ile Arg Tyr Ile Phe Thr Ala Thr Pro
35 40 45

Ala Lys Asp Phe Gly Gly Ile Phe His Thr Arg Tyr Glu Gln Ile His
50 55 60

Leu Val Pro Ala Glu Pro Pro Glu Ala Cys Gly Glu Leu Ser Asn Gly
65 70 75 80

Phe Phe Ile Gln Asp Gln Ile Ala Leu Val Glu Arg Gly Gly Cys Ser
85 90 95

Phe Leu Ser Lys Thr Arg Val Val Gln Glu His Gly Gly Arg Ala Val
100 105 110

Ile Ile Ser Asp Asn Ala Leu Thr Met Thr Ala Ser Thr Trp Arg
115 120 125

<210> 180
<211> 146
<212> PRT
<213> Homo sapiens

<400> 180
Met Gln Gln Ser Arg Leu Leu Leu Pro Phe Leu Phe Phe Leu Leu Glu
1 5 10 15

Gly Cys Ala Pro Ser Ser Leu Gly Pro Gly Ala Ala Pro Gly Ser Gly
20 25 30

```
His Ser Leu Gly Pro Pro Gly Ser Pro Gly Ala Pro Gly Pro Gln Pro
         35                  40                  45

Ala Val Gly Pro Ser Ser Pro Cys Gln Pro Gly Pro Ser Pro Ser Ser
     50                  55                  60

Pro Ala Ala Ala Ala Ala Ser Ser Gln Ser Ser Val Ala Ser Trp Pro
 65                  70                  75                  80

Cys Thr Leu Arg Cys Ala Ala Pro Ser Pro Asp Ala Ser Ala Leu Arg
                 85                  90                  95

Pro Ala Ala Ser Pro Ala Ala Thr Pro Ala Trp Ser Pro Gly Ser Gly
            100                 105                 110

Thr Ile Arg Val Leu Arg Pro Pro Ala Pro Ala Ala Ala Pro Ala Thr
        115                 120                 125

Ala Ile Thr Asn Arg Gly Pro Pro Arg Arg Arg Arg Arg Asn Ala Arg
    130                 135                 140

Thr Ala
145
```

<210> 181
<211> 68
<212> PRT
<213> Homo sapiens

<400> 181

```
Met Lys Pro Thr Arg Ser Leu Trp Ile Ser Phe Leu Met Cys Cys Trp
  1               5                  10                  15

Ile Trp Phe Ala Asn Ile Leu Leu Arg Ile Phe Ala Ser Val Phe Phe
             20                  25                  30

Arg Asp Ile Gly Leu Lys Phe Ser Phe Phe Cys Cys Val Ser Ala Arg
         35                  40                  45

Leu Trp Tyr Gln Asp Asp Ala Gly Leu Ile Asn Glu Leu Gly Arg Ile
     50                  55                  60

Pro Ser Phe Tyr
 65
```

<210> 182
<211> 51
<212> PRT
<213> Homo sapiens

<400> 182

```
Met Thr Pro Val Phe Arg Ala Trp Gly Leu Trp Val Tyr Val Leu Pro
  1               5                  10                  15

Thr Gly Phe Pro Gly Pro Cys Cys Met Met Leu Leu Glu Leu Phe Pro
             20                  25                  30

Lys Glu Ser Val Pro Gln Ala Tyr Gln Gly Ile Leu Leu Tyr Leu His
```

35 40 45

Phe Gly Phe
50

<210> 183
<211> 85
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (68)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 183
Met Gly Met Pro Leu Val Thr Val Thr Ala Ala Thr Phe Pro Thr Leu
1 5 10 15

Ser Cys Pro Pro Arg Ala Trp Pro Glu Val Glu Ala Pro Glu Ala Pro
20 25 30

Ala Leu Pro Val Val Pro Glu Leu Pro Glu Val Pro Met Glu Met Pro
35 40 45

Leu Val Leu Pro Pro Glu Leu Glu Leu Leu Ser Leu Glu Ala Val His
50 55 60

Arg Tyr Gln Xaa Gly Gly Thr Leu Met Gly Trp Thr Arg Ala Glu Ala
65 70 75 80

Ser Ala Asn Gly Ser
85

<210> 184
<211> 191
<212> PRT
<213> Homo sapiens

<400> 184
Met Gly Asp His Leu Asp Leu Leu Leu Gly Val Val Leu Met Ala Gly
1 5 10 15

Pro Val Phe Gly Ile Pro Ser Cys Ser Phe Asp Gly Arg Ile Ala Phe
20 25 30

Tyr Arg Phe Cys Asn Leu Thr Gln Val Pro Gln Val Leu Asn Thr Thr
35 40 45

Glu Arg Leu Leu Leu Ser Phe Asn Tyr Ile Arg Thr Val Thr Ala Ser
50 55 60

Ser Phe Pro Phe Leu Glu Gln Leu Gln Leu Leu Glu Leu Gly Ser Gln
65 70 75 80

Tyr Thr Pro Leu Thr Ile Asp Lys Glu Ala Phe Arg Asn Leu Pro Asn
85 90 95

Leu Arg Ile Leu Asp Leu Gly Ser Ser Lys Ile Tyr Phe Leu His Pro

100 105 110

Asp Ala Phe Gln Gly Leu Phe His Leu Phe Glu Leu Arg Leu Tyr Phe
115 120 125

Cys Gly Leu Ser Asp Ala Val Leu Lys Asp Gly Tyr Phe Arg Asn Leu
130 135 140

Lys Ala Leu Thr Arg Leu Asp Leu Ser Lys Asn Gln Ile Arg Ser Leu
145 150 155 160

Tyr Leu His Pro Ser Phe Gly Lys Leu Asn Ser Leu Lys Ser Ile Asp
165 170 175

Phe Ser Ser Asn Gln Ile Phe Leu Val Cys Glu His Glu Leu Glu
180 185 190

<210> 185
<211> 231
<212> PRT
<213> Homo sapiens

<400> 185
Met Trp Ala Leu Gln Leu Ser Leu Pro Thr Cys Gly Leu Ala Ala Leu
1 5 10 15

Leu Thr His Met Arg Pro Cys Ser Ser Pro Tyr Pro His Ala Gly Leu
20 25 30

Ala Ala Leu Leu Thr His Met Gly Pro Cys Arg Ser Pro Tyr Pro His
35 40 45

Gly Gly Leu Ala Ala Val Leu Thr His Met Arg Ala Leu Gln Leu Ser
50 55 60

Leu Pro Thr Trp Gly Leu Ala Ala Leu Leu Thr His Met Arg Pro Cys
65 70 75 80

Ser Ser Pro Tyr Pro His Ala Gly Leu Ala Cys Cys Trp Leu Trp Ser
85 90 95

Leu Ser Ser His Arg Ser Leu Gln Val Gln Ala Thr His Arg Leu Val
100 105 110

Val Arg Thr Ile Lys Asp Arg Val Met Leu Lys Val Leu Pro Gln Thr
115 120 125

Arg Arg Arg Gly Pro Phe Leu Ser Ser Cys Arg Asn Asp Val Met Arg
130 135 140

Asn Cys Val Pro Arg His Ala Val Leu Val Thr Thr Cys Val Phe Val
145 150 155 160

Ser Phe Pro Thr His Cys Lys Val Gly Ile Thr Gly Pro Ile Thr Gln
165 170 175

Val Lys Gln Lys Pro Gly Asn His Ser Ser Pro Cys Pro Val Ile Gln
180 185 190

Leu Val Ala Lys Ala Glu Phe Glu Leu Met Leu Pro Ser Val Pro Lys
195 200 205

Pro Val Tyr Leu Thr Leu Val Leu Ser Cys Trp Cys Leu Cys Asp Val
210 215 220

Pro Cys Leu Ser Val Ser Leu
225 230

<210> 186
<211> 68
<212> PRT
<213> Homo sapiens

<400> 186
Met Tyr Leu Glu Val Ala Val Arg Pro Phe Leu Ile Ile Val Ala Phe
1 5 10 15

Leu Gly Leu Ser Phe Leu Ala Leu Gln Met Pro Phe Trp Gln Gly Ser
20 25 30

Ala Val Gly His Leu Arg Ala Gly Gly Ala Gly Val Ala His Leu Ser
35 40 45

Gln Ala Gly Ile Ile Gln Ala Pro Val His Ser Gly Arg Glu Gly Gln
50 55 60

Pro Pro Pro Gly
65

<210> 187
<211> 211
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (100)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (103)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 187
Met Gly Glu Ala Ser Pro Pro Ala Pro Ala Arg Arg His Leu Leu Val
1 5 10 15

Leu Leu Leu Leu Leu Ser Thr Leu Val Ile Pro Ser Ala Ala Ala Pro
20 25 30

Ile His Asp Ala Asp Ala Gln Glu Ser Ser Leu Gly Leu Thr Gly Leu
35 40 45

Gln Ser Leu Leu Gln Gly Phe Ser Arg Leu Phe Leu Lys Gly Asn Leu
50 55 60

Leu Arg Gly Ile Asp Ser Leu Phe Ser Ala Pro Met Asp Phe Arg Gly

65 70 75 80

Leu Pro Gly Asn Tyr His Lys Glu Glu Asn Gln Glu His Gln Leu Gly
85 90 95

Asn Asn Thr Xaa Ser Ser Xaa Leu Gln Ile Asp Lys Val Pro Arg Met
100 105 110

Glu Glu Lys Glu Ala Leu Val Pro Ile Gln Lys Ala Thr Asp Ser Phe
115 120 125

His Thr Glu Leu His Pro Arg Val Ala Phe Trp Ile Ile Lys Leu Pro
130 135 140

Arg Arg Arg Ser His Gln Asp Ala Leu Glu Gly Gly His Trp Leu Ser
145 150 155 160

Glu Lys Arg His Arg Leu Gln Ala Ile Arg Asp Gly Leu Arg Lys Gly
165 170 175

Thr His Lys Asp Val Leu Glu Glu Gly Thr Glu Ser Ser Ser His Ser
180 185 190

Arg Leu Ser Pro Arg Lys Thr His Leu Leu Tyr Ile Leu Arg Pro Ser
195 200 205

Arg Gln Leu
210

<210> 188
<211> 90
<212> PRT
<213> Homo sapiens

<400> 188
Met Leu Val Val Ser Thr Val Ile Ile Val Phe Trp Glu Phe Ile Asn
1 5 10 15

Ser Thr Glu Gly Ser Phe Leu Trp Ile Tyr His Ser Lys Asn Pro Glu
20 25 30

Val Asp Asp Ser Ser Ala Gln Lys Gly Trp Trp Phe Leu Ser Trp Phe
35 40 45

Asn Asn Gly Ile His Asn Tyr Gln Gln Gly Glu Glu Asp Ile Asp Lys
50 55 60

Glu Lys Gly Arg Glu Glu Thr Lys Gly Arg Lys Met Thr Gln Gln Ser
65 70 75 80

Phe Gly Tyr Gly Thr Gly Leu Ile Gln Thr
85 90

<210> 189
<211> 62
<212> PRT
<213> Homo sapiens

<400> 189

119

Met Glu Leu Met Ala Leu Phe Phe Arg Thr Thr Thr Val Ala Ala Met
1 5 10 15

Ala Ser Arg Gly Ala Leu Ala Leu Phe Leu Arg Lys Ile Leu Ser Glu
20 25 30

Ala Lys Phe Lys Leu Ser Leu Thr Pro Gln Pro Pro Gln Pro Phe Tyr
35 40 45

Ile Tyr Met Ala Tyr Tyr Ser Glu Asn Phe Phe Leu Lys Phe
50 55 60

<210> 190
<211> 295
<212> PRT
<213> Homo sapiens

<400> 190
Met Leu Cys Cys Trp Phe Pro Trp Arg Ile Leu Ala Ala Gly Gln Val
1 5 10 15

Pro Tyr Ser Pro His Ser Pro Gln Val Ala Gly Cys Asp Leu Thr Arg
20 25 30

Cys Glu Ser Gly Gly Ala Arg Ala Leu Ser Ile Gln Arg Ala Ala Leu
35 40 45

Val Val Leu Glu Asn Tyr Tyr Lys Asp Phe Thr Ile Tyr Asn Pro Asn
50 55 60

Leu Leu Thr Ala Ser Lys Phe Arg Ala Ala Lys His Met Ala Gly Leu
65 70 75 80

Lys Val Tyr Asn Val Asp Gly Pro Ser Asn Asn Ala Thr Gly Gln Ser
85 90 95

Arg Ala Met Ile Ala Ala Ala Ala Arg Arg Arg Asp Ser Ser His Asn
100 105 110

Glu Leu Tyr Tyr Glu Glu Ala Glu His Glu Arg Arg Val Lys Lys Arg
115 120 125

Lys Ala Arg Leu Val Val Ala Val Glu Glu Ala Phe Ile His Ile Gln
130 135 140

Arg Leu Gln Ala Glu Glu Gln Gln Lys Ala Pro Gly Glu Val Met Asp
145 150 155 160

Pro Arg Glu Ala Ala Gln Ala Ile Phe Pro Ser Met Ala Arg Ala Leu
165 170 175

Gln Lys Tyr Leu Arg Ile Thr Arg Gln Gln Asn Tyr His Ser Met Glu
180 185 190

Ser Ile Leu Gln His Leu Ala Phe Cys Ile Thr Asn Gly Met Thr Pro
195 200 205

Lys Ala Phe Leu Glu Arg Tyr Leu Ser Ala Gly Pro Thr Leu Gln Tyr
210 215 220

```
Asp Lys Asp Arg Trp Leu Ser Thr Gln Trp Arg Leu Val Ser Asp Glu
225                 230                 235                 240

Ala Val Thr Asn Gly Leu Arg Asp Gly Ile Val Phe Val Leu Lys Cys
                245                 250                 255

Leu Asp Phe Ser Leu Val Val Asn Val Lys Lys Ile Pro Phe Ile Ile
            260                 265                 270

Leu Ser Glu Glu Phe Ile Asp Pro Lys Ser His Lys Phe Val Leu Arg
        275                 280                 285

Leu Gln Ser Glu Thr Ser Val
    290                 295
```

<210> 191
<211> 295
<212> PRT
<213> Homo sapiens

<400> 191

```
Met Gly Leu Pro Val Ser Trp Ala Pro Pro Ala Leu Trp Val Leu Gly
  1               5                  10                  15

Cys Cys Ala Leu Leu Leu Ser Leu Trp Ala Leu Cys Thr Ala Cys Arg
             20                  25                  30

Arg Pro Glu Asp Ala Val Ala Pro Arg Lys Arg Ala Arg Arg Gln Arg
         35                  40                  45

Ala Arg Leu Gln Gly Ser Ala Thr Ala Ala Glu Ala Ser Leu Leu Arg
     50                  55                  60

Arg Thr His Leu Cys Ser Leu Ser Lys Ser Asp Thr Arg Leu His Glu
 65                  70                  75                  80

Leu His Arg Gly Pro Arg Ser Ser Arg Ala Leu Arg Pro Ala Ser Met
                 85                  90                  95

Asp Leu Leu Arg Pro His Trp Leu Glu Val Ser Arg Asp Ile Thr Gly
            100                 105                 110

Pro Gln Ala Ala Pro Ser Ala Phe Pro His Gln Glu Leu Pro Arg Ala
        115                 120                 125

Leu Pro Ala Ala Ala Ala Thr Ala Gly Cys Ala Gly Leu Glu Ala Thr
    130                 135                 140

Tyr Ser Asn Val Gly Leu Ala Ala Leu Pro Gly Val Ser Leu Ala Ala
145                 150                 155                 160

Ser Pro Val Val Ala Glu Tyr Ala Arg Val Gln Lys Arg Lys Gly Thr
                165                 170                 175

His Arg Ser Pro Gln Glu Pro Gln Gln Gly Lys Thr Glu Val Thr Pro
            180                 185                 190

Ala Ala Gln Val Asp Val Leu Tyr Ser Arg Val Cys Lys Pro Lys Arg
```

195 200 205

Arg Asp Pro Gly Pro Thr Thr Asp Pro Leu Asp Pro Lys Gly Gln Gly
210 215 220

Ala Ile Leu Ala Leu Ala Gly Asp Leu Ala Tyr Gln Thr Leu Pro Leu
225 230 235 240

Arg Ala Leu Asp Val Asp Ser Gly Pro Leu Glu Asn Val Tyr Glu Ser
245 250 255

Ile Arg Glu Leu Gly Asp Pro Ala Gly Arg Ser Ser Thr Cys Gly Ala
260 265 270

Gly Thr Pro Pro Ala Ser Ser Cys Pro Ser Leu Gly Arg Gly Trp Arg
275 280 285

Pro Leu Pro Ala Ser Leu Pro
290 295

<210> 192
<211> 338
<212> PRT
<213> Homo sapiens

<400> 192
Met Met Arg Thr Cys Val Leu Leu Ser Ala Val Leu Trp Cys Leu Thr
1 5 10 15

Gly Val Gln Cys Pro Arg Phe Thr Leu Phe Asn Lys Lys Gly Phe Ile
20 25 30

Tyr Gly Lys Thr Gly Gln Pro Asp Lys Ile Tyr Val Glu Leu His Gln
35 40 45

Asn Ser Pro Val Leu Ile Cys Met Asp Phe Lys Leu Ser Lys Lys Glu
50 55 60

Ile Val Asp Pro Thr Tyr Leu Trp Ile Gly Pro Asn Glu Lys Thr Leu
65 70 75 80

Thr Gly Asn Asn Arg Ile Asn Ile Thr Glu Thr Gly Gln Leu Met Val
85 90 95

Lys Asp Phe Leu Glu Pro Leu Ser Gly Leu Tyr Thr Cys Thr Leu Ser
100 105 110

Tyr Lys Thr Val Lys Ala Glu Thr Gln Glu Glu Lys Thr Val Lys Lys
115 120 125

Arg Tyr Asp Phe Met Val Phe Ala Tyr Arg Glu Pro Asp Tyr Ser Tyr
130 135 140

Gln Met Ala Val Arg Phe Thr Thr Arg Ser Cys Ile Gly Arg Tyr Asn
145 150 155 160

Asp Val Phe Phe Arg Val Leu Lys Lys Ile Leu Asp Ile Leu Ile Ser
165 170 175

Asp Leu Ser Cys His Val Ile Glu Pro Ser Tyr Lys Cys His Ser Val
180 185 190

Glu Ile Pro Glu His Gly Leu Ile His Glu Leu Phe Ile Ala Phe Gln
195 200 205

Val Asn Pro Phe Ala Pro Gly Trp Lys Gly Ala Cys Asn Gly Ser Val
210 215 220

Asp Cys Glu Asp Thr Thr Asn His Asn Ile Leu Gln Ala Arg Asp Arg
225 230 235 240

Ile Glu Asp Phe Phe Arg Ser Gln Ala Tyr Ile Phe Tyr His Asn Phe
245 250 255

Asn Lys Thr Leu Pro Ala Met His Phe Val Asp His Ser Leu Gln Val
260 265 270

Val Arg Leu Asp Ser Cys Arg Pro Gly Phe Gly Lys Asn Glu Arg Leu
275 280 285

His Ser Asn Cys Ala Ser Cys Cys Val Val Cys Ser Pro Ala Thr Phe
290 295 300

Ser Pro Asp Val Asn Val Thr Cys Gln Thr Cys Val Ser Val Leu Thr
305 310 315 320

Tyr Gly Ala Lys Ser Cys Pro Gln Thr Ser Asn Lys Asn Gln Gln Tyr
325 330 335

Glu Asp

<210> 193
<211> 78
<212> PRT
<213> Homo sapiens

<400> 193
Met Gln Gln Arg Gly Ala Ala Gly Ser Arg Gly Cys Ala Leu Phe Pro
1 5 10 15

Leu Leu Gly Val Leu Phe Phe Gln Val Ser Ala Pro Ala Gly Tyr Ala
20 25 30

Pro Leu Pro Ala Gly Gly Leu Gly Lys Met Val Ala Phe Pro Val Pro
35 40 45

Gly Arg Gly Val Ser Arg Lys Pro Pro His Ser Ser Gly Lys Glu Gly
50 55 60

Gly Arg Glu Arg Asp Val Gly Thr Met Ser Ser Pro Pro Arg
65 70 75

<210> 194
<211> 181
<212> PRT
<213> Homo sapiens

<400> 194
Met Met Leu Met Pro Tyr Gly Ala Leu Ile Ile Gly Phe Val Cys Gly
1 5 10 15

Ile Ile Ser Thr Leu Gly Phe Val Tyr Leu Thr Pro Phe Leu Glu Ser
20 25 30

Arg Leu His Ile Gln Asp Thr Cys Gly Ile Asn Asn Leu His Gly Ile
35 40 45

Pro Gly Ile Ile Gly Gly Ile Val Gly Ala Val Thr Ala Ala Ser Ala
50 55 60

Ser Leu Glu Val Tyr Gly Lys Glu Gly Leu Val His Ser Phe Asp Phe
65 70 75 80

Gln Gly Phe Asn Gly Asp Trp Thr Ala Arg Thr Gln Gly Lys Phe Gln
85 90 95

Ile Tyr Gly Leu Leu Val Thr Leu Ala Met Ala Leu Met Gly Gly Ile
100 105 110

Ile Val Gly Leu Ile Leu Arg Leu Pro Phe Trp Gly Gln Pro Ser Asp
115 120 125

Glu Asn Cys Phe Glu Asp Ala Val Tyr Trp Glu Met Pro Glu Gly Asn
130 135 140

Ser Thr Val Tyr Ile Pro Glu Asp Pro Thr Phe Lys Pro Ser Gly Pro
145 150 155 160

Ser Val Pro Ser Val Pro Met Val Ser Pro Leu Pro Met Ala Ser Ser
165 170 175

Val Pro Leu Val Pro
180

<210> 195
<211> 79
<212> PRT
<213> Homo sapiens

<400> 195
Met Leu Ser Leu Asp Phe Leu Asp Asp Val Arg Arg Met Asn Lys Arg
1 5 10 15

Gln Val Ser Leu Ser Val Leu Phe Phe Ser Trp Leu Phe Leu Ser Leu
20 25 30

Arg Gly Cys Cys Cys Gly Ala Arg Arg Thr Pro Gly Phe Trp Cys Glu
35 40 45

Gly Leu Ser Trp Ser Asp Thr Arg Val Ile Arg Phe Leu Trp Arg Leu
50 55 60

Trp Pro Glu Ala Ala Leu Ser Ala Ser Leu Phe Leu Thr Pro Asn
65 70 75

<210> 196

<211> 69
<212> PRT
<213> Homo sapiens

<400> 196
Met Glu Pro Arg Ser Phe Leu Leu Pro Glu Leu Gly Gly Arg Val Ser
1 5 10 15

His Ile Pro Leu Gly Leu Thr Leu Val Phe Ala Cys Phe Leu Met Val
20 25 30

Arg Glu Thr Ala Gly Gly Phe Ser Phe Arg Ala Gly Asp Leu Glu Glu
35 40 45

Ile Ser Arg Lys Arg Thr Asn Val Leu Gly Ser Leu Arg Gly Thr Glu
50 55 60

Leu Ile Gly Tyr Ile
65

<210> 197
<211> 271
<212> PRT
<213> Homo sapiens

<400> 197
Met Thr Gln Gly Lys Leu Ser Val Ala Asn Lys Ala Pro Gly Thr Glu
1 5 10 15

Gly Gln Gln Gln Val His Gly Glu Lys Lys Glu Ala Pro Ala Val Pro
20 25 30

Ser Ala Pro Pro Ser Tyr Glu Glu Ala Thr Ser Gly Glu Gly Met Lys
35 40 45

Ala Gly Ala Phe Pro Pro Ala Pro Thr Ala Val Pro Leu His Pro Ser
50 55 60

Trp Ala Tyr Val Asp Pro Ser Ser Ser Ser Ser Tyr Asp Asn Gly Phe
65 70 75 80

Pro Thr Gly Asp His Glu Leu Phe Thr Thr Phe Ser Trp Asp Asp Gln
85 90 95

Lys Val Arg Arg Val Phe Val Arg Lys Val Tyr Thr Ile Leu Leu Ile
100 105 110

Gln Leu Leu Val Thr Leu Ala Val Val Ala Leu Phe Thr Phe Cys Asp
115 120 125

Pro Val Lys Asp Tyr Val Gln Ala Asn Pro Gly Trp Tyr Trp Ala Ser
130 135 140

Tyr Ala Val Phe Phe Ala Thr Tyr Leu Thr Leu Ala Cys Cys Ser Gly
145 150 155 160

Pro Arg Arg His Phe Pro Trp Glu Pro Asp Ser Pro Asp Arg Leu Tyr
165 170 175

```
                                                125
Pro Val His Gly Leu Pro His Trp Asp Ala Val Gln Leu Leu Gln His
            180                 185                 190

His Leu Arg Ala Ala Val Pro Gly His His Gly Pro Cys Leu Pro Leu
        195                 200                 205

Ser His Arg Leu Gln Leu Pro Asp Gln Val Arg Leu His Leu Leu Pro
    210                 215                 220

Gly Arg Ala Leu Arg Ala Ser His Asp Ser Phe Leu Gln Arg Thr His
225                 230                 235                 240

Pro Gly His Pro Pro Thr Leu Pro Ile Cys Ala Leu Ala Pro Cys Ser
                245                 250                 255

Leu Cys Ser Thr Gly Ser Gly Cys Ile Tyr Ile Val Pro Gly Thr
            260                 265                 270
```

<210> 198
<211> 51
<212> PRT
<213> Homo sapiens

<400> 198

```
Met Lys Cys Thr Ala Val Phe Ala Pro Ser Ala Trp Pro Asn Thr Leu
  1               5                  10                  15

Ser Leu Leu Val Ser Leu His Thr Val Met Cys Ile Asn Trp His Leu
             20                  25                  30

Val Ser Ala Ser His Met His Ile Gly Arg Ile Val Ile Leu Glu Gly
         35                  40                  45

Asp Gly Met
     50
```

<210> 199
<211> 71
<212> PRT
<213> Homo sapiens

<400> 199

```
Met Pro Asn Thr Phe His Thr Tyr Arg Pro Ile Leu Leu Leu Leu Leu
  1               5                  10                  15

Leu Pro Ser Ser Ser His Gln Asn Met Ile Val Ser Leu Pro Gln Asn
             20                  25                  30

Met Tyr Phe Leu Ile Ala Val Ala Lys Arg Leu Cys Ala Glu Ser Leu
         35                  40                  45

Ala Ser Asp Pro Ala Pro Cys Asn Leu Ser Ala Leu Gln Ala Lys Pro
     50                  55                  60

Arg Pro Arg Leu Arg His Tyr
 65                  70
```

<210> 200
<211> 60

<212> PRT
<213> Homo sapiens

<400> 200
Met Leu Tyr Trp Gly Asn Val Ala Leu Val Leu Pro Thr Pro Tyr Leu
1 5 10 15

His Leu Ser Leu Thr Leu Leu Leu Ser Pro Glu Trp Leu Gly Glu Met
20 25 30

Gly Arg Gly Leu Pro Trp Pro Gly His Leu Val Ala Ala Trp Leu Asp
35 40 45

His Ile Ala Asn Glu Leu Gly Arg Gly Ala Ile Phe
50 55 60

<210> 201
<211> 143
<212> PRT
<213> Homo sapiens

<400> 201
Met Lys Trp Glu Arg Gly Ser Pro Met Val Leu Leu Ala Leu Val Tyr
1 5 10 15

Asp Val Cys Cys Ala Ser Arg Arg Gly Gly Gln Ser His Pro Thr Ser
20 25 30

Gly Ser Asp Val Leu Pro Leu Pro Val Pro Ala Leu Ala Gln Pro Ala
35 40 45

Gln Pro Ser Arg Leu Asp Ala Cys Ala Lys Ala Arg Gly Ser Gln Arg
50 55 60

Ala Ala Gly Trp Pro Arg Ala Gly Ser Arg Leu Gly Pro Ala Val Gly
65 70 75 80

Arg Ala Ala Ser Pro Ser Ser Leu Gln Thr His Gly Ser Ser Ser Gln
85 90 95

Ser Ser Arg Gln Leu Pro Gly Pro Glu Met Ser Ser Ser Pro Pro Trp
100 105 110

Gly Gln Ala Leu Pro Trp Pro Ser Ser Val Asn Pro Ser Phe Leu Cys
115 120 125

Ala Val Ser Gly Leu Leu Thr Val Val Cys Val Cys Ala Arg Leu
130 135 140

<210> 202
<211> 148
<212> PRT
<213> Homo sapiens

<400> 202
Met Gln Phe Ile Leu Thr Gly Ile Thr Leu Ser Gly Tyr Leu Phe Thr
1 5 10 15

Phe Ser Ala Cys Ala Val Leu Ser Ala Ser Ile Thr Val Trp Gly Leu

20 25 30

Met Glu Cys Leu Ile His Arg His Gly Ser His Thr Thr Glu His Leu
35 40 45

Thr Arg Thr Leu Thr Ser Gln Gln Ser Ser Arg Gly His Leu Ser Leu
50 55 60

Ser His Ser Thr Thr Gln Ser Asn Gln Pro Glu Arg Thr Leu Ala Leu
65 70 75 80

Leu Thr Gly Gly Thr Ala Asp Leu Ser Val Trp Arg Gln His Ser Pro
85 90 95

Lys Met Gly Ala Ile Phe Gln Asp Ala Val Phe Ala Leu Asp Ser Gln
100 105 110

Ala Tyr Leu Trp Gly Ile Val Ser Asn Arg Glu Asn Ile Trp Val Leu
115 120 125

Glu Gln Trp Pro Pro Pro Lys Gly Phe His Ser Cys Gln Glu Thr Pro
130 135 140

Gln Glu Ser His
145

<210> 203
<211> 36
<212> PRT
<213> Homo sapiens

<400> 203
Met Trp Thr Cys Pro Gly Ile Ala Ala Leu Val Leu Met Ile Val Pro
1 5 10 15

Gly Cys Ser Leu Cys Pro Ala Gln Val Val His His Val Gly Gln Arg
20 25 30

Glu Ser Pro Ser
35

<210> 204
<211> 406
<212> PRT
<213> Homo sapiens

<400> 204
Met Ser Gly Ala Pro Thr Ala Gly Ala Ala Leu Met Leu Cys Ala Ala
1 5 10 15

Thr Ala Val Leu Leu Ser Ala Gln Gly Gly Pro Val Gln Ser Lys Ser
20 25 30

Pro Arg Phe Ala Ser Trp Asp Glu Met Asn Val Leu Ala His Gly Leu
35 40 45

Leu Gln Leu Gly Gln Gly Leu Arg Glu His Ala Glu Arg Thr Arg Ser
50 55 60

128

Gln Leu Ser Ala Leu Glu Arg Arg Leu Ser Ala Cys Gly Ser Ala Cys
65 70 75 80

Gln Gly Thr Glu Gly Ser Thr Asp Leu Pro Leu Ala Pro Glu Ser Arg
85 90 95

Val Asp Pro Glu Val Leu His Ser Leu Gln Thr Gln Leu Lys Ala Gln
100 105 110

Asn Ser Arg Ile Gln Gln Leu Phe His Lys Val Ala Gln Gln Gln Arg
115 120 125

His Leu Glu Lys Gln His Leu Arg Ile Gln His Leu Gln Ser Gln Phe
130 135 140

Gly Leu Leu Asp His Lys His Leu Asp His Glu Val Ala Lys Pro Ala
145 150 155 160

Arg Arg Lys Arg Leu Pro Glu Met Ala Gln Pro Val Asp Pro Ala His
165 170 175

Asn Val Ser Arg Leu His Arg Leu Pro Arg Asp Cys Gln Glu Leu Phe
180 185 190

Gln Val Gly Glu Arg Gln Ser Gly Leu Phe Glu Ile Gln Pro Gln Gly
195 200 205

Ser Pro Pro Phe Leu Val Asn Cys Lys Met Thr Ser Asp Gly Gly Trp
210 215 220

Thr Val Ile Gln Arg Arg His Asp Gly Ser Val Asp Phe Asn Arg Pro
225 230 235 240

Trp Glu Ala Tyr Lys Ala Gly Phe Gly Asp Pro His Gly Glu Phe Trp
245 250 255

Leu Gly Leu Glu Lys Val His Ser Ile Thr Gly Asp Arg Asn Ser Arg
260 265 270

Leu Ala Val Gln Leu Arg Asp Trp Asp Gly Asn Ala Glu Leu Leu Gln
275 280 285

Phe Ser Val His Leu Gly Gly Glu Asp Thr Ala Tyr Ser Leu Gln Leu
290 295 300

Thr Ala Pro Val Ala Gly Gln Leu Gly Ala Thr Thr Val Pro Pro Ser
305 310 315 320

Gly Leu Ser Val Pro Phe Ser Thr Trp Asp Gln Asp His Asp Leu Arg
325 330 335

Arg Asp Lys Asn Cys Ala Lys Ser Leu Ser Gly Gly Trp Trp Phe Gly
340 345 350

Thr Cys Ser His Ser Asn Leu Asn Gly Gln Tyr Phe Arg Ser Ile Pro
355 360 365

Gln Gln Arg Gln Lys Leu Lys Lys Gly Ile Phe Trp Lys Thr Trp Arg
370 375 380

Gly Arg Tyr Tyr Pro Leu Gln Ala Thr Thr Met Leu Ile Gln Pro Met
385 390 395 400

Ala Ala Glu Ala Ala Ser
405

<210> 205
<211> 91
<212> PRT
<213> Homo sapiens

<400> 205
Met Glu Lys Thr Leu Phe Leu Tyr His Tyr Leu Pro Ala Leu Thr Phe
1 5 10 15

Gln Ile Leu Leu Leu Pro Val Val Leu Gln His Ile Ser Asp His Leu
20 25 30

Cys Arg Ser Gln Leu Gln Arg Ser Ile Phe Ser Ala Leu Val Val Ala
35 40 45

Trp Tyr Ser Ser Ala Cys His Val Ser Asn Thr Leu Arg Pro Leu Thr
50 55 60

Tyr Gly Asp Lys Ser Leu Ser Pro His Glu Leu Lys Ala Leu Arg Trp
65 70 75 80

Lys Asp Ser Trp Asp Ile Leu Ile Arg Lys His
85 90

<210> 206
<211> 101
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (23)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (29)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 206
Met Leu Leu Phe Gly Leu Cys Trp Gly Pro Tyr Val Ala Thr Leu Leu
1 5 10 15

Leu Ser Val Leu Ala Tyr Xaa Gln Arg Pro Pro Leu Xaa Pro Gly Thr
20 25 30

Leu Leu Ser Leu Leu Ser Leu Gly Ser Ala Ser Ala Ala Ala Val Pro
35 40 45

Val Ala Met Gly Leu Gly Asp Gln Arg Tyr Thr Ala Pro Trp Arg Ala
50 55 60

```
                                                130
Ala Ala Gln Arg Cys Leu Gln Gly Leu Trp Gly Arg Ala Ser Arg Asp
 65                  70                  75                  80

Ser Pro Gly Pro Ser Ile Ala Tyr His Pro Ser Ser Gln Ser Ser Val
                85                  90                  95

Asp Leu Asp Leu Asn
            100
```

<210> 207
<211> 50
<212> PRT
<213> Homo sapiens

<400> 207

```
Met Ser Ala Gly Lys Trp Leu Leu Leu Val Ile Phe Arg Asp Leu Gly
  1               5                  10                  15

Cys Gly Val Ser Arg Thr Ser Pro His Leu Arg Ser Gly Glu Glu Gly
             20                  25                  30

Arg Ile Trp Ser Leu Leu Thr Ala Cys Ser Cys Cys Cys Leu Phe Val
         35                  40                  45

Ile Phe
     50
```

<210> 208
<211> 161
<212> PRT
<213> Homo sapiens

<400> 208

```
Met Thr Ser Ala Leu Arg Gly Val Ala Asp Asp Gln Gly Gln His Pro
  1               5                  10                  15

Leu Leu Lys Met Leu Leu His Leu Leu Ala Phe Ser Ser Ala Ala Thr
             20                  25                  30

Gly His Leu Gln Ala Ser Val Leu Thr Gln Cys Leu Lys Val Leu Val
         35                  40                  45

Lys Leu Ala Glu Asn Thr Ser Cys Asp Phe Leu Pro Arg Phe Gln Cys
     50                  55                  60

Val Phe Gln Val Leu Pro Lys Cys Leu Ser Pro Glu Thr Pro Leu Pro
 65                  70                  75                  80

Ser Val Leu Leu Ala Val Glu Leu Leu Ser Leu Leu Ala Asp His Asp
                85                  90                  95

Gln Leu Ala Pro Gln Leu Cys Ser His Ser Glu Gly Cys Leu Leu Leu
            100                 105                 110

Leu Leu Tyr Met Tyr Ile Thr Ser Arg Pro Asp Arg Val Ala Leu Glu
        115                 120                 125

Thr Gln Trp Leu Gln Leu Glu Gln Glu Val Val Trp Leu Leu Ala Lys
    130                 135                 140
```

Leu Gly Val Gln Glu Pro Leu Ala Pro Ser His Trp Leu Gln Leu Pro
145 150 155 160

Val

<210> 209
<211> 227
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (67)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (170)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 209
Met Leu Gly Leu Leu Leu Leu Cys Thr Pro Arg Ala Trp Leu Thr Leu
1 5 10 15

Ser Gly Pro Val Cys Phe Gln Gly Arg Gly Pro Ser Glu Val Pro Gln
20 25 30

Arg Pro Pro Gln Leu Trp Val Val Ser Ile Ser Val Leu Gln Gly Gln
35 40 45

His Arg Gly Arg Ala Gly Pro Arg Asp Glu Gln Glu Arg Gly Arg Asp
50 55 60

Gln His Xaa Leu Pro Ala His Gly Arg Leu His Leu Ser Pro Arg Pro
65 70 75 80

Glu Pro Gly Cys Arg Pro Ala Cys Ala Ala Pro Gly Gly Gln Pro Gly
85 90 95

Val Val Ser Gly Leu Pro Ala Leu Gly Gln Pro Arg Glu Ala Ser Ala
100 105 110

Pro Cys His Ile Ser Arg Leu Arg Thr Ala Ser Leu Ala Val Val Met
115 120 125

Gly Ala Glu Lys Gly Gly Ala Glu Met Arg Pro Trp Pro Ala Val Gln
130 135 140

Ala Pro Ala Pro Leu Pro Ser Val Gly Gly Thr Pro Ile Cys Ala Pro
145 150 155 160

Gly Cys Gly Ser Lys Asp Thr Val Pro Xaa Leu Gln Pro Ser Val Pro
165 170 175

Lys Gly Arg Ala Glu Ser Gly Phe Val Ser Ala Arg Phe Leu Cys Pro
180 185 190

His Pro Pro Arg Ser Leu Leu Cys Leu Gly Pro Gly Pro Ser Leu Ser
195 200 205

Gly Leu Pro Gly Pro Pro Ile Pro Ala Leu Leu Gln Gly Pro Leu Gly
210 215 220

Leu Gly Cys
225

<210> 210
<211> 351
<212> PRT
<213> Homo sapiens

<400> 210
Met Leu Thr Leu Arg Ser Leu Leu Phe Trp Ser Leu Val Tyr Cys Tyr
1 5 10 15

Cys Gly Leu Cys Ala Ser Ile His Leu Leu Lys Leu Leu Trp Ser Leu
20 25 30

Gly Lys Gly Pro Ala Gln Thr Phe Arg Arg Pro Ala Arg Glu His Pro
35 40 45

Pro Ala Cys Leu Ser Asp Pro Ser Leu Gly Thr His Cys Tyr Val Arg
50 55 60

Ile Lys Asp Ser Gly Leu Arg Phe His Tyr Val Ala Ala Gly Glu Arg
65 70 75 80

Gly Lys Pro Leu Met Leu Leu Leu His Gly Phe Pro Glu Phe Trp Tyr
85 90 95

Ser Trp Arg Tyr Gln Leu Arg Glu Phe Lys Ser Glu Tyr Arg Val Val
100 105 110

Ala Leu Asp Leu Arg Gly Tyr Gly Glu Thr Asp Ala Pro Ile His Arg
115 120 125

Gln Asn Tyr Lys Leu Asp Cys Leu Ile Thr Asp Ile Lys Asp Ile Leu
130 135 140

Asp Ser Leu Gly Tyr Ser Lys Cys Val Leu Ile Gly His Asp Trp Gly
145 150 155 160

Gly Met Ile Ala Trp Leu Ile Ala Ile Cys Tyr Pro Glu Met Val Met
165 170 175

Lys Leu Ile Val Ile Asn Phe Pro His Pro Asn Val Phe Thr Glu Tyr
180 185 190

Ile Leu Arg His Pro Ala Gln Leu Leu Lys Ser Ser Tyr Tyr Tyr Phe
195 200 205

Phe Gln Ile Pro Trp Phe Pro Glu Phe Met Phe Ser Ile Asn Asp Phe
210 215 220

Lys Val Leu Lys His Leu Phe Thr Ser His Ser Thr Gly Ile Gly Arg
225 230 235 240

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Lys Gly Cys Gln Leu Thr Thr Glu Asp Leu Glu Ala Tyr Ile Tyr Val
                245                 250                 255

Phe Ser Gln Pro Gly Ala Leu Ser Gly Pro Ile Asn His Tyr Arg Asn
            260                 265                 270

Ile Phe Ser Cys Leu Pro Leu Lys His His Met Val Thr Thr Pro Thr
        275                 280                 285

Leu Leu Leu Trp Gly Glu Asn Asp Ala Phe Met Glu Val Glu Met Ala
    290                 295                 300

Glu Val Thr Lys Ile Tyr Val Lys Asn Tyr Phe Arg Leu Thr Ile Leu
305                 310                 315                 320

Ser Glu Ala Ser His Trp Leu Gln Gln Asp Gln Pro Asp Ile Val Asn
                325                 330                 335

Lys Leu Ile Trp Thr Phe Leu Lys Glu Glu Thr Arg Lys Lys Asp
            340                 345                 350

<210> 211
<211> 93
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (59)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (61)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (84)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 211
Met Gly His Leu Pro His Ile Leu Ser Leu Gly Leu Phe Leu Thr Leu
  1               5                  10                  15

Leu Met Phe Cys Ile Thr Lys Ser Asp Gly Gln Asn Lys Ile Tyr Arg
             20                  25                  30

Cys Phe Lys Lys Ala Ser Pro Gln Val Ile Val Thr His Thr Lys Met
         35                  40                  45

Arg Ile Ala Ala Ile Ile Cys Ser Tyr Trp Xaa Gly Xaa Ala Asn Leu
     50                  55                  60

Gly Thr Arg Ile Lys Leu Gln Leu Asn Ser Ala Val Tyr Lys Ile Phe
 65                  70                  75                  80

Val Ser Leu Xaa Arg Lys Arg Lys Arg Thr Leu Ser Trp
```

85 90

<210> 212
<211> 101
<212> PRT
<213> Homo sapiens

<400> 212
Met Phe Gln Gln Gly Trp Ser Ser Pro Leu Leu Thr Pro Ala Phe Thr
1 5 10 15

Ile Leu Pro Met Ser Ser Leu Leu Thr Ser Leu His Pro Ala Pro Arg
20 25 30

Leu Pro Thr Leu Leu Ala Ala Ser Ser Pro Gln Leu Ala Pro Leu Thr
35 40 45

Cys Cys Phe Gln Tyr Pro Phe Leu Leu Ser Ala Ser Ser Leu Gly Asp
50 55 60

Ile His Pro Ser Ser Arg Asp Phe Ser Cys His Ile Asn Ser Asn Val
65 70 75 80

Ser Glu Leu Tyr Phe Leu Pro Pro Thr Ser Val Ser Leu Asn Val Arg
85 90 95

Ile Phe Tyr Phe Gln
100

<210> 213
<211> 98
<212> PRT
<213> Homo sapiens

<400> 213
Met Gly Trp Leu Gly Arg Thr Cys Leu Ala His Ser His Leu Asp Phe
1 5 10 15

Ile Ser Gly Ala Leu Leu Leu Thr Phe Ala Tyr Phe Leu Val Phe Gln
20 25 30

Val Cys Pro Val Ile Asn Lys Trp Leu Tyr Asn Leu Asp Gln His Val
35 40 45

Val Lys Glu Leu Ile Ser Lys Cys Trp Arg Trp Glu Gly Thr Gly Thr
50 55 60

Leu Gln Lys Lys Ala Gln Asn Pro Pro Ser Pro Phe Val Phe His Phe
65 70 75 80

Pro Leu Pro His Ser Gly Thr Ser Pro Arg Pro Lys Ile Ser Phe Leu
85 90 95

Leu Lys

<210> 214
<211> 81
<212> PRT

<213> Homo sapiens

<400> 214
Met Trp Gly Gly Ser Val Phe Leu Lys Pro Lys Leu Leu Gln Ala Gly
1 5 10 15

Gly Phe Leu His Phe Leu Phe Val Leu Phe Leu Thr Ala Asp Ser Val
20 25 30

His Leu Ser Val Gly Gly Glu Leu Leu Leu Arg Thr Gly Phe Lys Arg
35 40 45

His Ile Pro Val Thr Phe Lys Asn Leu His Gly Gly Arg Ser Phe Ser
50 55 60

Arg Ser Val Gly Trp Ser Thr Leu Gly Pro Thr Thr Leu Arg Arg Gly
65 70 75 80

Arg

<210> 215
<211> 188
<212> PRT
<213> Homo sapiens

<400> 215
Met Phe His Gln Ile Trp Ala Ala Leu Leu Tyr Phe Tyr Gly Ile Ile
1 5 10 15

Leu Asn Ser Ile Tyr Gln Cys Pro Glu His Ser Gln Leu Thr Thr Leu
20 25 30

Gly Val Asp Gly Lys Glu Phe Pro Glu Val His Leu Gly Gln Trp Tyr
35 40 45

Phe Ile Ala Gly Ala Ala Pro Thr Lys Glu Glu Leu Ala Thr Phe Asp
50 55 60

Pro Val Asp Asn Ile Val Phe Asn Met Ala Ala Gly Ser Ala Pro Met
65 70 75 80

Gln Leu His Leu Arg Ala Thr Ile Arg Met Lys Asp Gly Leu Cys Val
85 90 95

Pro Arg Lys Trp Ile Tyr His Leu Thr Glu Gly Ser Thr Asp Leu Arg
100 105 110

Thr Glu Gly Arg Pro Asp Met Lys Thr Glu Leu Phe Ser Ser Ser Cys
115 120 125

Pro Gly Gly Ile Met Leu Asn Glu Thr Gly Gln Gly Tyr Gln Arg Phe
130 135 140

Leu Leu Tyr Asn Arg Ser Pro His Pro Pro Glu Lys Cys Val Glu Glu
145 150 155 160

Phe Lys Ser Leu Thr Ser Cys Leu Asp Ser Lys Ala Phe Leu Leu Thr
165 170 175

Pro Arg Asn Gln Glu Ala Cys Glu Leu Ser Asn Asn
180 185

<210> 216
<211> 44
<212> PRT
<213> Homo sapiens

<400> 216
Met Gln Arg Thr Phe Lys Tyr Leu His Phe Tyr Ile Ile Arg Phe Val
1 5 10 15

Ser Thr Tyr Ala Phe Ile Val Phe Phe Pro Phe Ser Ser Ser His Val
20 25 30

Asn Gly Pro Cys Glu Lys Asn Ile Pro Leu Gly Lys
35 40

<210> 217
<211> 515
<212> PRT
<213> Homo sapiens

<400> 217
Met Gly Ser Ala Pro Trp Ala Pro Val Leu Leu Leu Ala Leu Gly Leu
1 5 10 15

Arg Gly Leu Gln Ala Gly Gly Glu Trp Arg Arg Pro Pro Ala His Ser
20 25 30

Pro Val Pro Ala Pro Pro Leu Arg Phe Ala Ser Pro His Ser Pro Gln
35 40 45

Ala Pro Asp Pro Gly Phe Gln Glu Arg Phe Phe Gln Gln Arg Leu Asp
50 55 60

His Phe Asn Phe Glu Arg Phe Gly Asn Lys Thr Phe Pro Gln Arg Phe
65 70 75 80

Leu Val Ser Asp Arg Phe Trp Val Arg Gly Glu Gly Pro Ile Phe Phe
85 90 95

Tyr Thr Gly Asn Glu Gly Asp Val Trp Ala Phe Ala Asn Asn Ser Gly
100 105 110

Phe Val Ala Glu Leu Ala Ala Glu Arg Gly Ala Leu Leu Val Phe Ala
115 120 125

Glu His Arg Tyr Tyr Gly Lys Ser Leu Pro Phe Gly Ala Gln Ser Thr
130 135 140

Gln Arg Gly His Thr Glu Leu Leu Thr Val Glu Gln Ala Leu Ala Asp
145 150 155 160

Phe Ala Glu Leu Leu Arg Ala Leu Arg Arg Asp Leu Gly Ala Gln Asp
165 170 175

Ala Pro Ala Ile Ala Phe Gly Gly Ser Tyr Gly Gly Met Leu Ser Ala

180 185 190

Tyr Leu Arg Met Lys Tyr Pro His Leu Val Ala Gly Ala Leu Ala Ala
195 200 205

Ser Ala Pro Val Leu Ala Val Ala Gly Leu Gly Asp Ser Asn Gln Phe
210 215 220

Phe Arg Asp Val Thr Ala Asp Phe Glu Gly Gln Ser Pro Lys Cys Thr
225 230 235 240

Gln Gly Val Arg Glu Ala Phe Arg Gln Ile Lys Asp Leu Phe Leu Gln
245 250 255

Gly Ala Tyr Asp Thr Val Arg Trp Glu Phe Gly Thr Cys Gln Pro Leu
260 265 270

Ser Asp Glu Lys Asp Leu Thr Gln Leu Phe Met Phe Ala Arg Asn Ala
275 280 285

Phe Thr Val Leu Ala Met Met Asp Tyr Pro Tyr Pro Thr Asp Phe Leu
290 295 300

Gly Pro Leu Pro Ala Asn Pro Val Lys Val Gly Cys Asp Arg Leu Leu
305 310 315 320

Ser Glu Ala Gln Arg Ile Thr Gly Leu Arg Ala Leu Ala Gly Leu Val
325 330 335

Tyr Asn Ala Ser Gly Ser Glu His Cys Tyr Asp Ile Tyr Arg Leu Tyr
340 345 350

His Ser Cys Ala Asp Pro Thr Gly Cys Gly Thr Gly Pro Asp Ala Arg
355 360 365

Ala Trp Asp Tyr Gln Ala Cys Thr Glu Ile Asn Leu Thr Phe Ala Ser
370 375 380

Asn Asn Val Thr Asp Met Phe Pro Asp Leu Pro Phe Thr Asp Glu Leu
385 390 395 400

Arg Gln Arg Tyr Cys Leu Asp Thr Trp Gly Val Trp Pro Arg Pro Asp
405 410 415

Trp Leu Leu Thr Ser Phe Trp Gly Gly Asp Leu Arg Ala Ala Ser Asn
420 425 430

Ile Ile Phe Ser Asn Gly Asn Leu Asp Pro Trp Ala Gly Gly Gly Ile
435 440 445

Arg Arg Asn Leu Ser Ala Ser Val Ile Ala Val Thr Ile Gln Gly Gly
450 455 460

Ala His His Leu Asp Leu Arg Ala Ser His Pro Glu Asp Pro Ala Ser
465 470 475 480

Val Val Glu Ala Arg Lys Leu Glu Ala Thr Ile Ile Gly Glu Trp Val
485 490 495

Lys Ala Ala Arg Arg Glu Gln Gln Pro Ala Leu Arg Gly Gly Pro Arg
500 505 510

Leu Ser Leu
515

<210> 218
<211> 522
<212> PRT
<213> Homo sapiens

<400> 218
Met Ala Ala Ala Met Pro Leu Ala Leu Leu Val Leu Leu Leu Leu Gly
1 5 10 15

Pro Gly Gly Trp Cys Leu Ala Glu Pro Pro Arg Asp Ser Leu Arg Glu
20 25 30

Glu Leu Val Ile Thr Pro Leu Pro Ser Gly Asp Val Ala Ala Thr Phe
35 40 45

Gln Phe Arg Thr Arg Trp Asp Ser Glu Leu Gln Arg Glu Gly Val Ser
50 55 60

His Tyr Arg Leu Phe Pro Lys Ala Leu Gly Gln Leu Ile Ser Lys Tyr
65 70 75 80

Ser Leu Arg Glu Leu His Leu Ser Phe Thr Gln Gly Phe Trp Arg Thr
85 90 95

Arg Tyr Trp Gly Pro Pro Phe Leu Gln Ala Pro Ser Asp Thr Asp His
100 105 110

Tyr Phe Leu Arg Tyr Ala Val Leu Pro Arg Glu Val Val Cys Thr Glu
115 120 125

Asn Leu Thr Pro Trp Lys Lys Leu Leu Pro Cys Ser Ser Lys Ala Gly
130 135 140

Leu Ser Val Leu Leu Lys Ala Asp Arg Leu Phe His Thr Ser Tyr His
145 150 155 160

Ser Gln Ala Val His Ile Arg Pro Val Cys Arg Asn Ala Arg Cys Thr
165 170 175

Ser Ile Ser Trp Glu Leu Arg Gln Thr Leu Ser Val Val Phe Asp Ala
180 185 190

Phe Ile Thr Gly Gln Gly Lys Lys Asp Trp Ser Leu Phe Arg Met Phe
195 200 205

Ser Arg Thr Leu Thr Glu Pro Cys Pro Leu Ala Ser Glu Ser Arg Val
210 215 220

Tyr Val Asp Ile Thr Thr Tyr Asn Gln Asp Asn Glu Thr Leu Glu Val
225 230 235 240

His Pro Pro Pro Thr Thr Thr Tyr Gln Asp Val Ile Leu Gly Thr Arg
245 250 255

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Lys Thr Tyr Ala Ile Tyr Asp Leu Leu Asp Thr Ala Met Ile Asn Asn
            260                 265                 270

Ser Arg Asn Leu Asn Ile Gln Leu Lys Trp Lys Arg Pro Pro Glu Asn
        275                 280                 285

Glu Ala Pro Pro Val Pro Phe Leu His Ala Gln Arg Tyr Val Ser Gly
    290                 295                 300

Tyr Gly Leu Gln Lys Gly Glu Leu Ser Thr Leu Leu Tyr Asn Thr His
305                 310                 315                 320

Pro Tyr Arg Ala Phe Pro Val Leu Leu Leu Asp Thr Val Pro Trp Tyr
                325                 330                 335

Leu Arg Leu Tyr Val His Thr Leu Thr Ile Thr Ser Lys Gly Lys Glu
            340                 345                 350

Asn Lys Pro Ser Tyr Ile His Tyr Gln Pro Ala Gln Asp Arg Leu Gln
        355                 360                 365

Pro His Leu Leu Glu Met Leu Ile Gln Leu Pro Ala Asn Ser Val Thr
    370                 375                 380

Lys Val Ser Ile Gln Phe Glu Arg Ala Leu Leu Lys Trp Thr Glu Tyr
385                 390                 395                 400

Thr Pro Asp Pro Asn His Gly Phe Tyr Val Ser Pro Ser Val Leu Ser
                405                 410                 415

Ala Leu Val Pro Ser Met Val Ala Ala Lys Pro Val Asp Trp Glu Glu
            420                 425                 430

Ser Pro Leu Phe Asn Ser Leu Phe Pro Val Ser Asp Gly Ser Asn Tyr
        435                 440                 445

Phe Val Arg Leu Tyr Thr Glu Pro Leu Leu Val Asn Leu Pro Thr Pro
    450                 455                 460

Asp Phe Ser Met Pro Tyr Asn Val Ile Cys Leu Thr Cys Thr Val Val
465                 470                 475                 480

Ala Val Cys Tyr Gly Ser Phe Tyr Asn Leu Leu Thr Arg Thr Phe His
                485                 490                 495

Ile Glu Glu Pro Arg Thr Gly Gly Leu Ala Lys Arg Leu Ala Asn Leu
            500                 505                 510

Ile Arg Arg Ala Arg Gly Val Pro Pro Leu
        515                 520
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<210> 219
<211> 52
<212> PRT
<213> Homo sapiens

<400> 219
Met Lys Ser His Ile Ser Trp Arg Leu Cys Ser Leu Leu Leu Ile Leu

140

1 5 10 15

Phe Ser Leu Ile Leu Ser Ala Cys Phe Ile Ser Ala Arg Trp Ser Ser
20 25 30

Asn Ser Asp Ile Phe Phe Ser Ala Trp Ser Ile Gln Leu Leu Ile Leu
35 40 45

Val Tyr Ala Ser
50

<210> 220
<211> 73
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (24)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 220
Met Gly Phe Trp Cys Gly Cys Pro Phe Cys Leu Leu Val Phe Leu Leu
1 5 10 15

Thr Val Arg Thr Arg Ser Phe Xaa Ser Val Gly Val Cys Trp Arg Ser
20 25 30

Thr Pro Asp Pro Leu Cys Leu Gly Ile Ser Ser Arg Ser Cys Arg Thr
35 40 45

Ala Asp Ile Gly Glu Gln Gln Met Leu Leu Pro Asp Arg Ser Ser Gly
50 55 60

Ser Phe Val Ser Glu Tyr Pro Ala Met
65 70

<210> 221
<211> 54
<212> PRT
<213> Homo sapiens

<400> 221
Met Tyr Arg Phe Phe Leu Cys Val Asp Leu Ser Phe Gln Leu Leu Trp
1 5 10 15

Val Ile Pro Arg Ser Thr Val Thr Gly Thr Tyr Gly Lys Asp Ile Phe
20 25 30

Ser Leu Ala Gly Asn His His Thr Val Phe Gln Ser Ser Cys Thr Ile
35 40 45

Leu His Thr His Gln His
50

<210> 222
<211> 72
<212> PRT
<213> Homo sapiens

<400> 222
Met Ala Thr Ile Leu Leu Lys Leu Pro Ile Leu Ser Ala Met Ile Lys
1 5 10 15

Lys Pro Leu Arg Asn Tyr Leu Lys Thr Ser Glu Thr Thr Met Glu Lys
20 25 30

Ile Ile Ile Gln Lys Leu Val Ala Asn Leu Lys Phe Leu Pro Leu Gly
35 40 45

Thr Leu Gln Leu Ala Met Met Ile Ala Asn Leu Ile Lys Lys Leu Phe
50 55 60

Phe Pro Leu Val Lys Ala Ala Lys
65 70

<210> 223
<211> 69
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (26)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (51)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (68)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 223
Met Tyr Leu Ala Val Tyr Leu Leu Leu Phe Leu Cys Ile Cys Phe Tyr
1 5 10 15

Phe Ile Ala Leu Phe Ser His Ala Leu Xaa Pro His Cys Phe Asn Tyr
20 25 30

Pro Gly Phe Ser Phe Asn Leu Val His Trp Ser Ser Leu Ile Pro Pro
35 40 45

Leu Pro Xaa Phe Phe Phe Phe Asn Ser Phe Ser Asn Cys Ser Leu Phe
50 55 60

Phe Pro Tyr Xaa Leu
65

<210> 224
<211> 57
<212> PRT
<213> Homo sapiens

<220>

<221> SITE
<222> (57)
<223> Xaa equals stop translation

<400> 224
Met Ala Lys Thr Asp Phe Ser Ile Ile Leu Leu Lys Leu His Cys Leu
1 5 10 15

Phe Phe Phe Ser Val Ile Ser Val His Cys Ala Gln Ser Phe Ile Ser
20 25 30

Val Thr Gln Thr Glu Pro Ser Pro Ala Val Cys Ile Phe Pro Ala Val
35 40 45

Gly Ser Gly Leu Gly Pro Cys Asp Xaa
50 55

<210> 225
<211> 77
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (77)
<223> Xaa equals stop translation

<400> 225
Met Ala Gly Pro Trp Thr Phe Thr Leu Leu Cys Gly Leu Leu Ala Ala
1 5 10 15

Thr Leu Ile Gln Ala Thr Leu Ser Pro Thr Ala Val Leu Ile Leu Gly
20 25 30

Pro Lys Val Ile Lys Glu Lys Leu Thr Gln Glu Leu Lys Asp His Asn
35 40 45

Ala Thr Ser Ile Leu Gln Gln Leu Pro Leu Leu Ser Ala Met Arg Glu
50 55 60

Lys Pro Ala Gly Ala Ser Leu Cys Trp Ala Ala Trp Xaa
65 70 75

<210> 226
<211> 45
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (45)
<223> Xaa equals stop translation

<400> 226
Met Asp Leu Tyr Phe Phe Leu Leu Ala Gly Ile Gln Ala Val Thr Ala
1 5 10 15

Leu Leu Phe Val Trp Ile Ala Gly Arg Tyr Glu Arg Ala Ser Gln Gly
20 25 30

Pro Ala Ser His Ser Arg Phe Ser Arg Asp Arg Gly Xaa
35 40 45

<210> 227
<211> 102
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (47)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (98)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (102)
<223> Xaa equals stop translation

<400> 227
Met Ser Trp Val Gln Ala Thr Leu Leu Ala Arg Gly Leu Cys Arg Ala
1 5 10 15

Trp Gly Gly Thr Cys Gly Ala Ala Leu Thr Gly Thr Ser Ile Ser Gln
20 25 30

Val Pro Arg Arg Leu Pro Arg Gly Leu His Cys Ser Ala Leu Xaa Ile
35 40 45

Ala Leu Asn Ser Pro Trp Phe Pro Ala His Arg Asn Pro Gly Arg Gly
50 55 60

Pro Pro Arg Leu Trp Cys Pro Leu Arg Thr Cys Leu Gly Arg Arg Leu
65 70 75 80

Val Gly Asn Gly Thr Arg Arg Ala Ser Cys Arg Arg Cys Arg Asn Leu
85 90 95

Arg Xaa Gln Arg Ala Xaa
100

<210> 228
<211> 132
<212> PRT
<213> Homo sapiens

<400> 228
Met Thr Tyr Phe Ser Gly Leu Leu Val Ile Leu Ala Phe Ala Ala Trp
1 5 10 15

Val Ala Leu Ala Glu Gly Leu Gly Val Ala Val Tyr Ala Ala Ala Val
20 25 30

Leu Leu Gly Ala Gly Cys Ala Thr Ile Leu Val Thr Ser Leu Ala Met

35 40 45

Thr Ala Asp Leu Ile Gly Pro His Thr Asn Ser Gly Ala Phe Val Tyr
50 55 60

Gly Ser Met Ser Phe Leu Asp Lys Val Ala Asn Gly Leu Ala Val Met
65 70 75 80

Ala Ile Gln Ser Leu His Pro Cys Pro Ser Glu Leu Cys Cys Arg Ala
85 90 95

Cys Val Ser Phe Tyr His Trp Ala Met Val Ala Val Thr Gly Gly Val
100 105 110

Gly Val Ala Ala Ala Leu Cys Leu Cys Ser Leu Leu Leu Trp Pro Thr
115 120 125

Arg Leu Arg Arg
130

<210> 229
<211> 66
<212> PRT
<213> Homo sapiens

<400> 229
Met Thr Tyr Phe Ser Gly Leu Leu Val Ile Leu Ala Phe Ala Ala Trp
1 5 10 15

Val Ala Leu Ala Glu Gly Leu Gly Val Ala Val Tyr Ala Ala Ala Val
20 25 30

Leu Leu Gly Ala Gly Cys Ala Thr Ile Leu Val Thr Ser Leu Ala Met
35 40 45

Thr Ala Asp Leu Ile Gly Pro His Thr Asn Ser Gly Leu Ser Cys Thr
50 55 60

Ala Pro
65

<210> 230
<211> 73
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (73)
<223> Xaa equals stop translation

<400> 230
Met Pro Trp Lys Arg Ala Val Val Leu Leu Met Leu Trp Phe Ile Gly
1 5 10 15

Gln Ala Met Trp Leu Ala Pro Ala Tyr Val Leu Glu Phe Gln Gly Lys
20 25 30

Asn Thr Phe Leu Phe Ile Trp Leu Ala Gly Leu Phe Phe Leu Leu Ile

145

35 40 45

Asn Cys Ser Ile Leu Ile Gln Ile Ile Ser His Tyr Lys Glu Glu Pro
50 55 60

Leu Thr Glu Arg Ile Lys Tyr Asp Xaa
65 70

<210> 231
<211> 293
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (134)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 231
Met Leu Ala Leu Thr Phe Met Phe Met Val Leu Glu Val Val Val Ser
1 5 10 15

Arg Val Thr Ser Ser Leu Ala Met Leu Ser Asp Ser Phe His Met Leu
20 25 30

Ser Asp Val Leu Ala Leu Val Val Ala Leu Val Ala Glu Arg Phe Ala
35 40 45

Arg Arg Thr His Ala Thr Gln Lys Asn Thr Phe Gly Trp Ile Arg Ala
50 55 60

Glu Val Met Gly Ala Leu Val Asn Ala Ile Phe Leu Thr Gly Leu Cys
65 70 75 80

Phe Ala Ile Leu Leu Glu Ala Ile Glu Arg Phe Ile Glu Pro His Glu
85 90 95

Met Gln Gln Pro Leu Val Val Leu Gly Val Gly Val Ala Gly Leu Leu
100 105 110

Val Asn Val Leu Gly Leu Cys Leu Phe His His His Ser Gly Phe Ser
115 120 125

Gln Asp Ser Gly His Xaa His Ser His Gly Gly His Gly His Gly His
130 135 140

Gly Leu Pro Lys Gly Pro Arg Val Lys Ser Thr Arg Pro Gly Ser Ser
145 150 155 160

Asp Ile Asn Val Ala Pro Gly Glu Gln Gly Pro Asp Gln Glu Glu Thr
165 170 175

Asn Thr Leu Val Ala Asn Thr Ser Asn Ser Asn Gly Leu Lys Leu Asp
180 185 190

Pro Ala Asp Pro Glu Asn Pro Arg Ser Gly Asp Thr Val Glu Val Gln
195 200 205

Val Asn Gly Asn Leu Val Arg Glu Pro Asp His Met Glu Leu Glu Glu

210 215 220

Asp Arg Ala Gly Gln Leu Asn Met Arg Gly Val Phe Leu His Val Leu
225 230 235 240

Gly Asp Ala Leu Gly Ser Val Ile Val Val Val Asn Ala Leu Val Phe
245 250 255

Tyr Phe Ser Trp Lys Gly Cys Ser Glu Gly Asp Phe Cys Val Asn Pro
260 265 270

Cys Phe Pro Asp Pro Cys Lys Ala Phe Val Glu Ile Leu Ile Val Leu
275 280 285

Met His Gln Phe Met
290

<210> 232
<211> 55
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (55)
<223> Xaa equals stop translation

<400> 232
Met Lys Thr His Leu Leu Met Phe Leu Leu Ser Cys Met Ala Arg Cys
1 5 10 15

Thr Gly Ile Val Pro Lys Arg Pro Gln Pro Ala Phe Pro Leu Arg Gly
20 25 30

Arg Arg Arg Lys Asn Ser Phe Leu Phe Leu Leu Ser Phe Ser Ile Glu
35 40 45

Phe Leu Leu Cys Val Trp Xaa
50 55

<210> 233
<211> 47
<212> PRT
<213> Homo sapiens

<400> 233
Met Lys Thr His Leu Leu Met Phe Leu Leu Ser Cys Met Ala Arg Cys
1 5 10 15

Thr Gly Ile Val Pro Lys Arg Pro Gln Pro Ala Phe Pro Leu Arg Gly
20 25 30

Lys Glu Lys Lys Lys Leu Leu Phe Ile Phe Thr Phe Phe Gln His
35 40 45

<210> 234
<211> 54
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (41)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (54)
<223> Xaa equals stop translation

<400> 234
Met Cys Lys Ala Val Cys Lys His Arg Leu Arg Leu Phe Ala Val Ser
1 5 10 15

Ser Phe Ser Leu Gly Leu Gly Trp Val Cys Val Leu Val Leu Met Leu
20 25 30

Trp Pro Val Arg Leu Ser Leu Ala Xaa Arg Pro Val Gln Leu Gln Gln
35 40 45

Arg Arg Ser His Cys Xaa
50

<210> 235
<211> 70
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (70)
<223> Xaa equals stop translation

<400> 235
Met Ser Arg Lys Ser Leu Ala Phe Pro Ile Ile Cys Ser Tyr Leu Cys
1 5 10 15

Phe Leu Thr Val Ala Thr Cys Ser Ile Ala Cys Thr Thr Val Phe Phe
20 25 30

Ala Asn Leu Arg His Thr Arg Tyr Ile Cys Ile Glu Leu Ser Ala Leu
35 40 45

Glu Thr Ser Gly Val Ile Ser Pro Gln Ile Asn Asn Val Pro Glu Val
50 55 60

His Gly Lys Tyr Ser Xaa
65 70

<210> 236
<211> 69
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (69)
<223> Xaa equals stop translation

<400> 236
Met Lys Pro Thr Arg Ser Leu Trp Ile Ser Phe Leu Met Cys Cys Trp
1 5 10 15

Ile Trp Phe Ala Asn Ile Leu Leu Arg Ile Phe Ala Ser Val Phe Phe
20 25 30

Arg Asp Ile Gly Leu Lys Phe Ser Phe Phe Cys Cys Val Ser Ala Arg
35 40 45

Leu Trp Tyr Gln Asp Asp Ala Gly Leu Ile Asn Glu Leu Gly Arg Ile
50 55 60

Pro Ser Phe Tyr Xaa
65

<210> 237
<211> 67
<212> PRT
<213> Homo sapiens

<400> 237
Met Gly Glu Ala Ser Pro Pro Ala Pro Ala Arg Arg His Leu Leu Val
1 5 10 15

Leu Leu Leu Leu Leu Ser Thr Leu Val Ile Pro Ser Ala Ala Ala Pro
20 25 30

Ile His Asp Ala Asp Ala Gln Glu Ser Ser Leu Gly Leu Thr Gly Leu
35 40 45

Gln Ser Leu Leu Gln Gly Phe Ser Arg Leu Phe Leu Lys Val Thr Cys
50 55 60

Phe Gly Ala
65

<210> 238
<211> 90
<212> PRT
<213> Homo sapiens

<400> 238
Met Leu Val Val Ser Thr Val Ile Ile Val Phe Trp Glu Phe Ile Asn
1 5 10 15

Ser Thr Glu Gly Ser Phe Leu Trp Ile Tyr His Ser Lys Asn Pro Glu
20 25 30

Val Asp Asp Ser Ser Ala Gln Lys Gly Trp Trp Phe Leu Ser Trp Phe
35 40 45

Asn Asn Gly Ile His Asn Tyr Gln Gln Gly Glu Glu Asp Ile Asp Lys
50 55 60

Glu Lys Gly Arg Glu Glu Thr Lys Gly Arg Lys Met Thr Gln Gln Ser
65 70 75 80

149

Phe Gly Tyr Gly Thr Gly Leu Ile Gln Thr
85 90

<210> 239
<211> 140
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (117)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 239
Met Ala Phe Lys Leu Leu Ile Leu Leu Ile Gly Thr Trp Ala Leu Phe
1 5 10 15

Phe Arg Lys Arg Arg Ala Asp Met Pro Arg Val Phe Val Phe Arg Ala
20 25 30

Leu Leu Leu Val Leu Ile Phe Leu Phe Cys Gly Phe Pro Ile Gly Phe
35 40 45

Phe Thr Gly Ser Ala Phe Trp Thr Leu Gly Asn Arg Asn Tyr Gln Gly
50 55 60

Ile Val Gln Tyr Ala Val Ser Pro Cys Gly Met Pro Ser Ser Phe His
65 70 75 80

Pro Leu Leu Ala Ile Arg Pro Cys Trp Ser Ser Gly Ser Leu Gln Pro
85 90 95

Asn Val Pro Arg Cys Arg Leu Val Pro Leu Pro Thr Glu Trp Gly Asn
100 105 110

Pro Arg Phe Gln Xaa Gly Thr Pro Glu Tyr Pro Ala Ser Ser Ile Gly
115 120 125

Gly Pro Arg Lys Leu Leu Gln Arg Phe His His Leu
130 135 140

<210> 240
<211> 37
<212> PRT
<213> Homo sapiens

<400> 240
Met Gly Leu Pro Val Ser Trp Ala Pro Pro Ala Leu Trp Val Leu Gly
1 5 10 15

Cys Cys Ala Leu Leu Leu Ser Leu Trp Ala Leu Cys Thr Ala Cys Arg
20 25 30

Ser Pro Arg Thr Leu
35

<210> 241
<211> 21
<212> PRT

<213> Homo sapiens

<220>
<221> SITE
<222> (21)
<223> Xaa equals stop translation

<400> 241
Arg Leu Leu Asn Leu Ser Val Pro Met Phe Thr Phe Ile Val Val Lys
1 5 10 15

Arg Tyr Ala Thr Xaa
20

<210> 242
<211> 138
<212> PRT
<213> Homo sapiens

<400> 242
Met Ala Tyr Leu Thr Gly Met Leu Ser Ser Tyr Tyr Asn Thr Thr Ser
1 5 10 15

Val Leu Leu Cys Leu Gly Ile Thr Ala Leu Val Cys Leu Ser Val Thr
20 25 30

Val Phe Ser Phe Gln Thr Lys Phe Asp Phe Thr Ser Cys Gln Gly Val
35 40 45

Leu Phe Val Leu Leu Met Thr Leu Phe Phe Ser Gly Leu Ile Leu Ala
50 55 60

Ile Leu Leu Pro Phe Gln Tyr Val Pro Trp Leu His Ala Val Tyr Ala
65 70 75 80

Ala Leu Gly Ala Gly Val Phe Thr Leu Phe Leu Ala Leu Asp Thr Gln
85 90 95

Leu Leu Met Gly Asn Arg Arg His Ser Leu Ser Pro Glu Glu Tyr Ile
100 105 110

Phe Gly Ala Leu Asn Ile Tyr Leu Asp Ile Ile Tyr Ile Phe Thr Phe
115 120 125

Phe Leu Gln Leu Phe Gly Thr Asn Arg Glu
130 135

<210> 243
<211> 175
<212> PRT
<213> Homo sapiens

<400> 243
Met Ala Gln Trp Thr Ser Thr Gly Pro Gly Lys Pro Thr Arg Arg Gly
1 5 10 15

Leu Gly Ile Pro Thr Ala Ser Ser Gly Trp Val Trp Arg Arg Cys Ile
20 25 30

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                                                151
Ala Ser Trp Gly Thr Ala Thr Ala Ala Trp Pro Cys Ser Cys Gly Thr
          35                  40                  45

Gly Met Ala Thr Pro Ser Cys Cys Ser Ser Pro Cys Thr Trp Val Ala
      50                  55                  60

Arg Thr Arg Pro Ile Ala Cys Ser Ser Leu His Pro Trp Pro Ala Ser
 65                  70                  75                  80

Trp Ala Pro Pro Pro Ser His Pro Ala Ala Ser Pro Tyr Pro Ser Pro
                 85                  90                  95

Leu Gly Thr Arg Ile Thr Thr Ser Ala Gly Thr Arg Thr Ala Pro Arg
            100                 105                 110

Ala Ser Leu Glu Ala Gly Gly Leu Ala Pro Ala Ala Ile Pro Thr Phe
        115                 120                 125

Asn Gly Pro Val Leu Pro Ala Pro Ser His Ser Ser Gly Arg Ser Leu
    130                 135                 140

Arg Arg Glu Ser Ser Gly Arg Pro Ala Gly Arg Tyr Tyr Pro Leu Gln
145                 150                 155                 160

Ala Thr Thr Met Leu Ile Gln Pro Met Ala Ala Glu Ala Ala Ser
                165                 170                 175
```

<210> 244
<211> 39
<212> PRT
<213> Homo sapiens

<400> 244

```
Met Leu Gly Leu Leu Leu Leu Cys Thr Pro Arg Ala Trp Leu Thr Leu
  1               5                  10                  15

Ser Gly Pro Val Cys Phe Gln Gly Arg Asp Pro Leu Arg Ser His Arg
            20                  25                  30

Gly His Pro Ser Cys Gly Ser
        35
```

<210> 245
<211> 47
<212> PRT
<213> Homo sapiens

<400> 245

```
Met Leu Ser Ile Ile Pro Asn Asp Arg Leu Phe Ile Asn Leu Ile Phe
  1               5                  10                  15

Leu Ser Asn Phe Leu Pro Ser Val Leu Trp Glu Pro Ala Gly Gln Met
            20                  25                  30

Trp Tyr Thr His Val Arg Tyr Pro Ser Gly Arg Leu Leu Ser Leu
        35                  40                  45
```

<210> 246
<211> 34

<212> PRT
<213> Homo sapiens

<400> 246
Met Thr Gly Phe Ala Gln Phe Cys Val Ile Leu Gly Leu Asn Leu Ser
1 5 10 15

Leu Phe Gly Thr Phe Pro Tyr Leu Leu Pro Ser Ser Glu Ser Arg Cys
20 25 30

Arg Lys

<210> 247
<211> 490
<212> PRT
<213> Homo sapiens

<400> 247
Met Gly Ser Ala Pro Trp Ala Pro Val Leu Leu Leu Ala Leu Gly Leu
1 5 10 15

Arg Gly Leu Gln Ala Gly Ala Arg Ser Gly Pro Arg Leu Pro Gly Ala
20 25 30

Leu Leu Pro Ala Ala Ser Gly Pro Leu Gln Leu Arg Ala Leu Arg Gln
35 40 45

Gln Asp Leu Pro Ser Ala Leu Pro Gly Val Gly Gln Val Leu Gly Pro
50 55 60

Gly Arg Gly Ala His Leu Leu Leu His Trp Glu Arg Gly Arg Arg Val
65 70 75 80

Gly Leu Arg Gln Gln Leu Gly Leu Arg Arg Gly Leu Ala Ala Glu Arg
85 90 95

Gly Ala Leu Leu Val Phe Ala Glu His Arg Tyr Tyr Gly Lys Ser Leu
100 105 110

Pro Phe Gly Ala Gln Ser Thr Gln Arg Gly His Thr Glu Leu Leu Thr
115 120 125

Val Glu Gln Ala Leu Ala Asp Phe Ala Glu Leu Leu Arg Ala Leu Arg
130 135 140

Arg Asp Leu Gly Ala Gln Asp Ala Pro Ala Ile Ala Phe Gly Gly Ser
145 150 155 160

Tyr Gly Gly Met Leu Ser Ala Tyr Leu Arg Met Lys Tyr Pro His Leu
165 170 175

Val Ala Gly Ala Leu Ala Ala Ser Ala Pro Val Leu Ser Val Ala Gly
180 185 190

Leu Gly Asp Ser Asn Gln Phe Phe Arg Asp Val Thr Ala Asp Phe Glu
195 200 205

Gly Gln Ser Pro Lys Cys Thr Gln Gly Val Arg Glu Ala Phe Arg Gln

210 215 220

Ile Lys Asp Leu Phe Leu Gln Gly Ala Tyr Asp Thr Val Arg Trp Glu
225 230 235 240

Phe Gly Thr Cys Gln Pro Leu Ser Asp Glu Lys Asp Leu Thr Gln Leu
245 250 255

Phe Met Phe Ala Arg Asn Ala Phe Thr Val Leu Ala Met Met Asp Tyr
260 265 270

Pro Tyr Pro Thr Asp Phe Leu Gly Pro Leu Pro Ala Asn Pro Val Lys
275 280 285

Val Gly Cys Asp Arg Leu Leu Ser Glu Ala Gln Arg Ile Thr Gly Leu
290 295 300

Arg Ala Leu Ala Gly Leu Val Tyr Asn Ala Ser Gly Ser Glu His Cys
305 310 315 320

Tyr Asp Ile Tyr Arg Leu Tyr His Ser Cys Ala Asp Pro Thr Gly Cys
325 330 335

Gly Thr Gly Pro Asp Ala Arg Ala Trp Asp Tyr Gln Ala Cys Thr Glu
340 345 350

Ile Asn Leu Thr Phe Ala Ser Asn Asn Val Thr Asp Met Phe Pro Asp
355 360 365

Leu Pro Phe Thr Asp Glu Leu Arg Gln Arg Tyr Cys Leu Asp Thr Trp
370 375 380

Gly Val Trp Pro Arg Pro Asp Trp Leu Leu Thr Ser Phe Trp Gly Gly
385 390 395 400

Asp Leu Arg Ala Ala Ser Asn Ile Ile Phe Ser Asn Gly Asn Leu Asp
405 410 415

Pro Trp Ala Gly Gly Gly Ile Arg Arg Asn Leu Ser Ala Ser Val Ile
420 425 430

Ala Val Thr Ile Gln Gly Gly Ala His His Leu Asp Leu Arg Ala Ser
435 440 445

His Pro Glu Asp Pro Ala Ser Val Val Glu Ala Arg Lys Leu Glu Ala
450 455 460

Thr Ile Ile Gly Glu Trp Val Lys Ala Ala Arg Arg Glu Gln Gln Pro
465 470 475 480

Ala Leu Arg Gly Gly Pro Arg Leu Ser Leu
485 490

<210> 248
<211> 555
<212> PRT
<213> Homo sapiens

<220>

<221> SITE
<222> (555)
<223> Xaa equals stop translation

<400> 248

```
Gly Gly Gly Tyr Ala Leu Ala Leu Leu Val Leu Leu Leu Leu Gly Pro
  1               5                  10                  15

Gly Gly Trp Cys Leu Ala Glu Pro Pro Arg Asp Ser Leu Arg Glu Glu
             20                  25                  30

Leu Val Ile Thr Pro Leu Pro Ser Gly Asp Val Ala Ala Thr Phe Gln
         35                  40                  45

Phe Arg Thr Arg Trp Asp Ser Glu Leu Gln Arg Glu Gly Val Ser His
     50                  55                  60

Tyr Arg Leu Phe Pro Lys Ala Leu Gly Gln Leu Ile Ser Lys Tyr Ser
 65                  70                  75                  80

Leu Arg Glu Leu His Leu Ser Phe Thr Gln Gly Phe Trp Arg Thr Arg
                 85                  90                  95

Tyr Trp Gly Pro Pro Phe Leu Gln Ala Pro Ser Asp Thr Asp His Tyr
            100                 105                 110

Phe Leu Arg Tyr Ala Val Leu Pro Arg Glu Val Val Cys Thr Glu Asn
        115                 120                 125

Leu Thr Pro Trp Lys Lys Leu Leu Pro Cys Ser Ser Lys Ala Gly Leu
    130                 135                 140

Ser Val Leu Leu Lys Ala Asp Arg Leu Phe His Thr Ser Tyr His Ser
145                 150                 155                 160

Gln Ala Val His Ile Arg Pro Val Cys Arg Asn Ala Arg Cys Thr Ser
                165                 170                 175

Ile Ser Trp Glu Leu Arg Gln Thr Leu Ser Val Val Phe Asp Ala Phe
            180                 185                 190

Ile Thr Gly Gln Gly Lys Lys Asp Trp Ser Leu Phe Arg Met Phe Ser
        195                 200                 205

Arg Thr Leu Thr Glu Pro Cys Pro Leu Ala Ser Glu Ser Arg Val Tyr
    210                 215                 220

Val Asp Ile Thr Thr Tyr Asn Gln Asp Asn Glu Thr Leu Glu Val His
225                 230                 235                 240

Pro Pro Pro Thr Thr Thr Tyr Gln Asp Val Ile Leu Gly Thr Arg Lys
                245                 250                 255

Thr Tyr Ala Ile Tyr Asp Leu Leu Asp Thr Ala Met Ile Asn Asn Ser
            260                 265                 270

Arg Asn Leu Asn Ile Gln Leu Lys Trp Lys Arg Pro Pro Glu Asn Glu
        275                 280                 285
```

155

Ala Pro Pro Val Pro Phe Leu His Ala Gln Arg Tyr Val Ser Gly Tyr
290 295 300

Gly Leu Gln Lys Gly Glu Leu Ser Thr Leu Leu Tyr Asn Thr His Pro
305 310 315 320

Tyr Arg Ala Phe Pro Val Leu Leu Leu Asp Thr Val Pro Trp Tyr Leu
325 330 335

Arg Leu Tyr Val His Thr Leu Thr Ile Thr Ser Lys Gly Lys Glu Asn
340 345 350

Lys Pro Ser Tyr Ile His Tyr Gln Pro Ala Gln Asp Arg Leu Gln Pro
355 360 365

His Leu Leu Glu Met Leu Ile Gln Leu Pro Ala Asn Ser Val Thr Lys
370 375 380

Val Ser Ile Gln Phe Glu Arg Ala Leu Leu Lys Trp Thr Glu Tyr Thr
385 390 395 400

Pro Asp Pro Asn His Gly Phe Tyr Val Ser Pro Ser Val Leu Ser Ala
405 410 415

Leu Val Pro Ser Met Val Ala Ala Lys Pro Val Asp Trp Glu Glu Ser
420 425 430

Pro Leu Phe Asn Ser Leu Phe Pro Val Ser Asp Gly Ser Asn Tyr Phe
435 440 445

Val Arg Leu Tyr Thr Glu Pro Leu Leu Val Asn Leu Pro Thr Pro Asp
450 455 460

Phe Ser Met Pro Tyr Asn Val Ile Cys Leu Thr Cys Thr Val Val Ala
465 470 475 480

Val Cys Tyr Gly Ser Phe Tyr Asn Leu Leu Thr Arg Thr Phe Pro His
485 490 495

Arg Gly Ala Pro His Arg Trp Pro Gly Gln Ala Ala Gly Gln Pro Tyr
500 505 510

Pro Ala Arg Pro Ser Val Pro Pro Thr Leu Ile Leu Ala Leu Ser Ser
515 520 525

Ser Cys Ser Cys Arg Phe Ser Leu Gly Arg Gly Ala Gln Gly Leu Phe
530 535 540

Leu Pro Leu Ala Leu Leu Arg Val Gly Phe Xaa
545 550 555

<210> 249
<211> 21
<212> PRT
<213> Homo sapiens

<400> 249
Thr Arg Pro Glu Lys Val Gln Ala Pro Leu Lys Trp Phe Lys Phe Gln
1 5 10 15

Ile Leu Asp Pro Pro
20

<210> 250
<211> 272
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (51)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (229)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 250
Ser Ala Glu Phe Gly Val Ala Pro Leu Pro Gly Arg Arg Gly Ser Pro
1 5 10 15

Val Arg Gln Leu Ala Gln Phe Arg Arg Arg Leu Leu Arg Gly Ser Gly
20 25 30

Gly Arg Gly Ala Pro Gly Arg Pro Pro Arg Cys Pro Gly Glu Ala Arg
35 40 45

Val Met Xaa Pro Pro Ser Cys Ile Gln Asp Glu Pro Phe Pro His Pro
50 55 60

Leu Glu Pro Glu Pro Gly Val Ser Ala Gln Pro Gly Pro Gly Lys Pro
65 70 75 80

Ser Asp Lys Arg Phe Arg Leu Trp Tyr Val Gly Gly Ser Cys Leu Asp
85 90 95

His Arg Thr Thr Leu Pro Met Leu Pro Trp Leu Met Ala Glu Ile Arg
100 105 110

Arg Arg Ser Gln Lys Pro Glu Ala Gly Gly Cys Gly Ala Pro Ala Ala
115 120 125

Arg Glu Val Ile Leu Val Leu Ser Ala Pro Phe Leu Arg Cys Val Pro
130 135 140

Ala Pro Gly Ala Gly Ala Ser Gly Gly Thr Ser Pro Ser Ala Thr Gln
145 150 155 160

Pro Asn Pro Ala Val Phe Ile Phe Glu His Lys Ala Gln His Ile Ser
165 170 175

Arg Phe Ile His Asn Ser His Asp Leu Thr Tyr Phe Ala Tyr Leu Ile
180 185 190

Lys Ala Gln Pro Asp Asp Pro Glu Ser Gln Met Ala Cys His Val Phe
195 200 205

Arg Ala Thr Asp Pro Ser Gln Val Pro Asp Val Ile Ser Ser Ile Arg
210 215 220

Gln Leu Ser Lys Xaa Ala Met Lys Glu Asp Ala Lys Pro Ser Lys Asp
225 230 235 240

Asn Glu Asp Ala Phe Tyr Asn Ser Gln Lys Phe Glu Val Leu Tyr Cys
245 250 255

Gly Lys Val Thr Val Thr Pro Gln Glu Gly Pro Leu Lys Pro His Arg
260 265 270

<210> 251
<211> 14
<212> PRT
<213> Homo sapiens

<400> 251
Pro Met Leu Pro Trp Leu Met Ala Glu Ile Arg Arg Arg Ser
1 5 10

<210> 252
<211> 19
<212> PRT
<213> Homo sapiens

<400> 252
Ile His Asn Ser His Asp Leu Thr Tyr Phe Ala Tyr Leu Ile Lys Ala
1 5 10 15

Gln Pro Asp

<210> 253
<211> 12
<212> PRT
<213> Homo sapiens

<400> 253
Lys Phe Glu Val Leu Tyr Cys Gly Lys Val Thr Val
1 5 10

<210> 254
<211> 13
<212> PRT
<213> Homo sapiens

<400> 254
Ile Ser Ser Ile Arg Gln Leu Ser Lys Ala Met Lys Glu
1 5 10

<210> 255
<211> 20
<212> PRT
<213> Homo sapiens

<400> 255
Gly Glu Arg Arg Asn Trp Gly Gly Glu Val Tyr Tyr Ser Thr Gly Tyr
1 5 10 15

Ser Ser Arg Lys
20

<210> 256
<211> 9
<212> PRT
<213> Homo sapiens

<400> 256
Glu Pro Gly Ala Ala Gln Glu Ser Trp
1 5

<210> 257
<211> 202
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (108)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (120)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (138)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (165)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 257
Leu Cys Ala Arg Pro Ser Cys Ser Tyr Thr Gly Ala Glu Asn Gln Gly
1 5 10 15

Gln Pro Arg Ser Pro Gly Trp Gly Ser Ser His Val Gly Trp Gly Trp
20 25 30

Gly Val Gly Ser Pro Phe Leu Gly Ser Gln Glu Trp Ser Gly Leu Ala
35 40 45

Pro Asp Leu Pro Asp Gln Glu Glu Glu Gln Pro Val Gly Arg His Ser
50 55 60

Cys Pro Asp Met Ser Gln Cys Ile Lys Arg Gly His Gln Pro Val Gly
65 70 75 80

Phe Ser Lys His Ala Trp Arg Cys Leu Val Gly Cys Cys Pro Trp Glu
85 90 95

Glu Glu Lys Arg Ser Cys His Pro Phe Gly Ala Xaa Leu Leu Trp Val
100 105 110

Leu Arg Phe Ala Leu Gln Pro Xaa Val Tyr Glu Asp Pro Ala Ala Leu
115 120 125

Asp Gly Gly Glu Glu Gly Met Asp Ile Xaa Thr His Ile Leu Ala Leu
130 135 140

Ala Pro Arg Leu Leu Lys Asp Ser Gly Ser Ile Phe Leu Glu Val Asp
145 150 155 160

Pro Arg His Pro Xaa Leu Val Ser Ser Trp Leu Gln Ser Arg Pro Asp
165 170 175

Leu Tyr Leu Asn Leu Val Ala Val Arg Arg Asp Phe Cys Gly Arg Pro
180 185 190

Arg Phe Leu His Ile Arg Arg Ser Gly Pro
195 200

<210> 258
<211> 37
<212> PRT
<213> Homo sapiens

<400> 258
Leu Cys Ala Arg Pro Ser Cys Ser Tyr Thr Gly Ala Glu Asn Gln Gly
1 5 10 15

Gln Pro Arg Ser Pro Gly Trp Gly Ser Ser His Val Gly Trp Gly Trp
20 25 30

Gly Val Gly Ser Pro
35

<210> 259
<211> 37
<212> PRT
<213> Homo sapiens

<400> 259
Phe Leu Gly Ser Gln Glu Trp Ser Gly Leu Ala Pro Asp Leu Pro Asp
1 5 10 15

Gln Glu Glu Glu Gln Pro Val Gly Arg His Ser Cys Pro Asp Met Ser
20 25 30

Gln Cys Ile Lys Arg
35

<210> 260
<211> 37
<212> PRT
<213> Homo sapiens

<220>
<221> SITE

<222> (34)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 260
Gly His Gln Pro Val Gly Phe Ser Lys His Ala Trp Arg Cys Leu Val
1 5 10 15

Gly Cys Cys Pro Trp Glu Glu Glu Lys Arg Ser Cys His Pro Phe Gly
20 25 30

Ala Xaa Leu Leu Trp
35

<210> 261
<211> 37
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (9)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (27)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 261
Val Leu Arg Phe Ala Leu Gln Pro Xaa Val Tyr Glu Asp Pro Ala Ala
1 5 10 15

Leu Asp Gly Gly Glu Glu Gly Met Asp Ile Xaa Thr His Ile Leu Ala
20 25 30

Leu Ala Pro Arg Leu
35

<210> 262
<211> 54
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (17)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 262
Leu Lys Asp Ser Gly Ser Ile Phe Leu Glu Val Asp Pro Arg His Pro
1 5 10 15

Xaa Leu Val Ser Ser Trp Leu Gln Ser Arg Pro Asp Leu Tyr Leu Asn
20 25 30

Leu Val Ala Val Arg Arg Asp Phe Cys Gly Arg Pro Arg Phe Leu His
35 40 45

Ile Arg Arg Ser Gly Pro

50

<210> 263
<211> 19
<212> PRT
<213> Homo sapiens

<400> 263
Gln Glu Leu Leu Val Lys Ile Pro Leu Asp Met Val Ala Gly Phe Asn
1 5 10 15

Thr Pro Leu

<210> 264
<211> 26
<212> PRT
<213> Homo sapiens

<400> 264
Leu Arg Ile Gln Leu Leu His Lys Leu Ser Phe Leu Val Asn Ala Leu
1 5 10 15

Ala Lys Gln Val Met Asn Leu Leu Val Pro
20 25

<210> 265
<211> 20
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (2)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (10)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 265
His Xaa Ile Trp Leu Lys Val Ile Thr Xaa Asn Ile Leu Gln Leu Gln
1 5 10 15

Val Lys Pro Ser
20

<210> 266
<211> 58
<212> PRT
<213> Homo sapiens

<400> 266
Ala Gly Pro Trp Thr Phe Thr Leu Leu Cys Gly Leu Leu Ala Ala Thr
1 5 10 15

Leu Ile Gln Ala Thr Leu Ser Pro Thr Ala Val Leu Ile Leu Gly Pro
20 25 30

Lys Val Ile Lys Glu Lys Leu Thr Gln Glu Leu Lys Asp His Asn Ala
35 40 45

Thr Ser Ile Leu Gln Gln Leu Pro Leu Leu
50 55

<210> 267
<211> 15
<212> PRT
<213> Homo sapiens

<400> 267
His Phe Ile Ile Thr Leu Thr Thr Phe Phe Thr Asn Tyr Phe Leu
1 5 10 15

<210> 268
<211> 99
<212> PRT
<213> Homo sapiens

<400> 268
Met Lys Ile Thr Phe Gln Asp Leu Phe Pro Met Trp Asn Ser Phe Lys
1 5 10 15

Cys Phe Leu His Gly Asn Val Phe Ser Leu Phe Val Leu Phe Pro Leu
20 25 30

Leu Thr Cys Phe Ser Phe Pro Tyr Thr Val Asn Ser Gly Thr Lys Leu
35 40 45

Asp Trp Val Gly Trp Leu Val Gly Trp Phe Phe Leu Glu Phe Met Tyr
50 55 60

Ile Asn Lys Gly Phe Glu Val Thr Ser Glu Asn Asn Ile Ser Lys Arg
65 70 75 80

Val Leu Val Arg Glu Asn Ile Arg Ile Lys Ser Ser Pro Glu Arg Val
85 90 95

Leu Arg Met

<210> 269
<211> 19
<212> PRT
<213> Homo sapiens

<400> 269
Arg Phe Trp Gly Ser Tyr Glu Pro His Phe Ser Gln Glu Val Ser Val
1 5 10 15

Ile Pro Pro

<210> 270
<211> 56
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (32)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 270
Ile Arg Gly Asn Tyr Phe Ser Gly Arg Lys Lys Ser Ser Ser Asp Thr
1 5 10 15

Pro Lys Gly Ser Lys Asp Lys Ile Ser Val Trp Asn Arg Ser Gln Xaa
20 25 30

Ala Cys Ile Arg Ile Cys Lys Val His Pro Asn Tyr Ile Gln Ile Tyr
35 40 45

Leu Trp His Ser Ala Thr Ser Phe
50 55

<210> 271
<211> 74
<212> PRT
<213> Homo sapiens

<400> 271
Ala Gly Asn Gln Val Glu Pro Phe His Val Ser Leu Pro Ser Cys Leu
1 5 10 15

Ser Pro Leu Pro His Leu Gly His Ser Met Gly Val Pro Ser Pro Thr
20 25 30

Ala Trp Pro Ser Leu Ala Ser Phe His Thr Gln Lys Lys Ala Arg Ile
35 40 45

Arg Gln Glu Glu Glu Ser Pro Pro Leu Pro Ser Pro Gln Glu Leu Ala
50 55 60

Phe Ser Ala Leu Arg Val Phe Phe Arg Val
65 70

<210> 272
<211> 38
<212> PRT
<213> Homo sapiens

<400> 272
Phe Ile Gln Gln Asn Ile Ser Phe Leu Leu Gly Tyr Ser Ile Pro Val
1 5 10 15

Gly Cys Val Gly Leu Ala Phe Phe Ile Phe Leu Phe Ala Thr Pro Val
20 25 30

Phe Ile Thr Lys Pro Pro
35

<210> 273
<211> 347
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (16)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (340)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (341)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 273

```
Val Ser Ala His His Pro Ser Gly Ala Asp Glu Gly Val Thr Ala Xaa
  1               5                  10                  15

Gln Ile Leu Pro Thr Glu Glu Tyr Glu Glu Ala Met Ser Thr Met Gln
             20                  25                  30

Val Ser Gln Leu Asp Leu Phe Arg Leu Leu Asp Gln Asn Arg Asp Gly
         35                  40                  45

His Leu Gln Leu Arg Glu Val Leu Ala Gln Thr Arg Leu Gly Asn Gly
     50                  55                  60

Trp Trp Met Thr Pro Glu Ser Ile Gln Glu Met Tyr Ala Ala Ile Lys
 65                  70                  75                  80

Ala Asp Pro Asp Gly Asp Gly Val Leu Ser Leu Gln Glu Phe Ser Asn
                 85                  90                  95

Met Asp Leu Arg Asp Phe His Lys Tyr Met Arg Ser His Lys Ala Glu
            100                 105                 110

Ser Ser Glu Leu Val Arg Asn Ser His His Thr Trp Leu Tyr Gln Gly
        115                 120                 125

Glu Gly Ala His His Ile Met Arg Ala Ile Arg Gln Arg Val Leu Arg
    130                 135                 140

Leu Thr Arg Leu Ser Pro Glu Ile Val Glu Leu Ser Glu Pro Leu Gln
145                 150                 155                 160

Val Val Arg Tyr Gly Glu Gly Gly His Tyr His Ala His Val Asp Ser
                165                 170                 175

Gly Pro Val Tyr Pro Glu Thr Ile Cys Ser His Thr Lys Leu Val Ala
            180                 185                 190

Asn Glu Ser Val Pro Phe Glu Thr Ser Cys Arg Tyr Met Thr Val Leu
        195                 200                 205

Phe Tyr Leu Asn Asn Val Thr Gly Gly Gly Glu Thr Val Phe Pro Val
    210                 215                 220
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                                                165
Ala Asp Asn Arg Thr Tyr Asp Glu Met Ser Leu Ile Gln Asp Asp Val
225                 230                 235                 240

Asp Leu Arg Asp Thr Arg Arg His Cys Asp Lys Gly Asn Leu Arg Val
                245                 250                 255

Lys Pro Gln Gln Gly Thr Ala Val Phe Trp Tyr Asn Tyr Leu Pro Asp
            260                 265                 270

Gly Gln Gly Trp Val Gly Asp Val Asp Asp Tyr Ser Leu His Gly Gly
        275                 280                 285

Cys Leu Val Thr Arg Gly Thr Lys Trp Ile Ala Asn Asn Trp Ile Asn
    290                 295                 300

Val Asp Pro Ser Arg Ala Arg Gln Ala Leu Phe Gln Gln Glu Met Ala
305                 310                 315                 320

Arg Leu Ala Arg Glu Gly Gly Thr Asp Ser Gln Pro Glu Trp Ala Leu
                325                 330                 335

Asp Arg Ala Xaa Xaa Asp Ala Arg Val Glu Leu
            340                 345
```

<210> 274
<211> 6
<212> PRT
<213> Homo sapiens

<400> 274
Ala Val Phe Trp Tyr Asn
1 5

<210> 275
<211> 18
<212> PRT
<213> Homo sapiens

<400> 275
Thr Val Leu Phe Tyr Leu Asn Asn Val Thr Gly Gly Gly Glu Thr Val
1 5 10 15

Phe Pro

<210> 276
<211> 59
<212> PRT
<213> Homo sapiens

<400> 276
Asp Leu Phe Arg Leu Leu Asp Gln Asn Arg Asp Gly His Leu Gln Leu
1 5 10 15

Arg Glu Val Leu Ala Gln Thr Arg Leu Gly Asn Gly Trp Trp Met Thr
20 25 30

Pro Glu Ser Ile Gln Glu Met Tyr Ala Ala Ile Lys Ala Asp Pro Asp
35 40 45

Gly Asp Gly Val Leu Ser Leu Gln Glu Phe Ser
50 55

<210> 277
<211> 38
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (16)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 277
Val Ser Ala His His Pro Ser Gly Ala Asp Glu Gly Val Thr Ala Xaa
1 5 10 15

Gln Ile Leu Pro Thr Glu Glu Tyr Glu Glu Ala Met Ser Thr Met Gln
20 25 30

Val Ser Gln Leu Asp Leu
35

<210> 278
<211> 38
<212> PRT
<213> Homo sapiens

<400> 278
Phe Arg Leu Leu Asp Gln Asn Arg Asp Gly His Leu Gln Leu Arg Glu
1 5 10 15

Val Leu Ala Gln Thr Arg Leu Gly Asn Gly Trp Trp Met Thr Pro Glu
20 25 30

Ser Ile Gln Glu Met Tyr
35

<210> 279
<211> 38
<212> PRT
<213> Homo sapiens

<400> 279
Ala Ala Ile Lys Ala Asp Pro Asp Gly Asp Gly Val Leu Ser Leu Gln
1 5 10 15

Glu Phe Ser Asn Met Asp Leu Arg Asp Phe His Lys Tyr Met Arg Ser
20 25 30

His Lys Ala Glu Ser Ser
35

<210> 280
<211> 38
<212> PRT
<213> Homo sapiens

<400> 280
Glu Leu Val Arg Asn Ser His His Thr Trp Leu Tyr Gln Gly Glu Gly
1 5 10 15

Ala His His Ile Met Arg Ala Ile Arg Gln Arg Val Leu Arg Leu Thr
20 25 30

Arg Leu Ser Pro Glu Ile
35

<210> 281
<211> 38
<212> PRT
<213> Homo sapiens

<400> 281
Val Glu Leu Ser Glu Pro Leu Gln Val Val Arg Tyr Gly Glu Gly Gly
1 5 10 15

His Tyr His Ala His Val Asp Ser Gly Pro Val Tyr Pro Glu Thr Ile
20 25 30

Cys Ser His Thr Lys Leu
35

<210> 282
<211> 38
<212> PRT
<213> Homo sapiens

<400> 282
Val Ala Asn Glu Ser Val Pro Phe Glu Thr Ser Cys Arg Tyr Met Thr
1 5 10 15

Val Leu Phe Tyr Leu Asn Asn Val Thr Gly Gly Gly Glu Thr Val Phe
20 25 30

Pro Val Ala Asp Asn Arg
35

<210> 283
<211> 38
<212> PRT
<213> Homo sapiens

<400> 283
Thr Tyr Asp Glu Met Ser Leu Ile Gln Asp Asp Val Asp Leu Arg Asp
1 5 10 15

Thr Arg Arg His Cys Asp Lys Gly Asn Leu Arg Val Lys Pro Gln Gln
20 25 30

Gly Thr Ala Val Phe Trp
35

<210> 284
<211> 38
<212> PRT
<213> Homo sapiens

<400> 284
Tyr Asn Tyr Leu Pro Asp Gly Gln Gly Trp Val Gly Asp Val Asp Asp
1 5 10 15

Tyr Ser Leu His Gly Gly Cys Leu Val Thr Arg Gly Thr Lys Trp Ile
20 25 30

Ala Asn Asn Trp Ile Asn
35

<210> 285
<211> 43
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (36)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (37)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 285
Val Asp Pro Ser Arg Ala Arg Gln Ala Leu Phe Gln Gln Glu Met Ala
1 5 10 15

Arg Leu Ala Arg Glu Gly Gly Thr Asp Ser Gln Pro Glu Trp Ala Leu
20 25 30

Asp Arg Ala Xaa Xaa Asp Ala Arg Val Glu Leu
35 40

<210> 286
<211> 15
<212> PRT
<213> Homo sapiens

<400> 286
Leu Leu Ala Asp Leu Met Arg Asn Tyr Asp Pro His Leu Arg Pro
1 5 10 15

<210> 287
<211> 19
<212> PRT
<213> Homo sapiens

<400> 287
Ile Ser Val Thr Tyr Phe Pro Phe Asp Trp Gln Asn Cys Ser Leu Ile
1 5 10 15

Phe Gln Ser

<210> 288
<211> 16

<212> PRT
<213> Homo sapiens

<400> 288
Ser Met Ala Arg Gly Val Arg Lys Val Phe Leu Arg Leu Leu Pro Gln
1 5 10 15

<210> 289
<211> 18
<212> PRT
<213> Homo sapiens

<400> 289
Gln Ala Ser Pro Ala Ile Gln Ala Cys Val Asp Ala Cys Asn Leu Met
1 5 10 15

Ala Arg

<210> 290
<211> 17
<212> PRT
<213> Homo sapiens

<400> 290
Tyr Asn Gln Val Pro Asp Leu Pro Phe Pro Gly Asp Pro Arg Pro Tyr
1 5 10 15

Leu

<210> 291
<211> 15
<212> PRT
<213> Homo sapiens

<400> 291
Cys Ser Ile Ser Val Thr Tyr Phe Pro Phe Asp Trp Gln Asn Cys
1 5 10 15

<210> 292
<211> 18
<212> PRT
<213> Homo sapiens

<400> 292
Val Leu Lys Tyr Ala Leu Phe Leu Val Leu Lys Asn Tyr Tyr Tyr Cys
1 5 10 15

Pro Tyr

<210> 293
<211> 315
<212> PRT
<213> Homo sapiens

<400> 293

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Met Arg Glu Tyr Gly Val Glu Arg Asp Leu Ala Val Tyr Asn Gln Leu
  1               5                  10                  15

Leu Asn Ile Phe Pro Lys Glu Val Phe Arg Pro Arg Asn Ile Ile Gln
             20                  25                  30

Arg Ile Phe Val His Tyr Pro Arg Gln Gln Glu Cys Gly Ile Ala Val
         35                  40                  45

Leu Glu Gln Met Glu Asn His Gly Val Met Pro Asn Lys Glu Thr Glu
     50                  55                  60

Phe Leu Leu Ile Gln Ile Phe Gly Arg Lys Ser Tyr Pro Met Leu Lys
 65                  70                  75                  80

Leu Val Arg Leu Lys Leu Trp Phe Pro Arg Phe Met Asn Val Asn Pro
                 85                  90                  95

Phe Pro Val Pro Arg Asp Leu Pro Gln Asp Pro Val Glu Leu Ala Met
            100                 105                 110

Phe Gly Leu Arg His Met Glu Pro Asp Leu Ser Ala Arg Val Thr Ile
        115                 120                 125

Tyr Gln Val Pro Leu Pro Lys Asp Ser Thr Gly Ala Ala Asp Pro Pro
    130                 135                 140

Gln Pro His Ile Val Gly Ile Gln Ser Pro Asp Gln Gln Ala Ala Leu
145                 150                 155                 160

Ala Arg His Asn Pro Ala Arg Pro Val Phe Val Glu Gly Pro Phe Ser
                165                 170                 175

Leu Trp Leu Arg Asn Lys Cys Val Tyr Tyr His Ile Leu Arg Ala Asp
            180                 185                 190

Leu Leu Pro Pro Glu Glu Arg Glu Val Glu Glu Thr Pro Glu Glu Trp
        195                 200                 205

Asn Leu Tyr Tyr Pro Met Gln Leu Asp Leu Glu Tyr Val Arg Ser Gly
    210                 215                 220

Trp Asp Asn Tyr Glu Phe Asp Ile Asn Glu Val Glu Glu Gly Pro Val
225                 230                 235                 240

Phe Ala Met Cys Met Ala Gly Ala His Asp Gln Ala Thr Met Ala Lys
                245                 250                 255

Trp Ile Gln Gly Leu Gln Glu Thr Asn Pro Thr Leu Ala Gln Ile Pro
            260                 265                 270

Val Val Phe Arg Leu Ala Gly Ser Thr Arg Glu Leu Gln Thr Ser Ser
        275                 280                 285

Ala Gly Leu Glu Glu Pro Pro Leu Pro Glu Asp His Gln Glu Glu Asp
    290                 295                 300
```

Asp Asn Leu Gln Arg Gln Gln Gln Gly Gln Ser
305 310 315

<210> 294
<211> 19
<212> PRT
<213> Homo sapiens

<400> 294
Phe Gln Phe Gly Trp Ala Ser Thr Gln Ile Ser His Leu Ser Leu Ile
1 5 10 15

Pro Glu Leu

<210> 295
<211> 14
<212> PRT
<213> Homo sapiens

<400> 295
Leu Arg Tyr Ala Phe Thr Val Val Ala Asn Ile Thr Val Tyr
1 5 10

<210> 296
<211> 17
<212> PRT
<213> Homo sapiens

<400> 296
Phe Val Tyr Gly Ser Met Ser Phe Leu Asp Lys Val Ala Asn Gly Leu
1 5 10 15

Ala

<210> 297
<211> 17
<212> PRT
<213> Homo sapiens

<400> 297
Trp His Leu Val Gly Thr Val Cys Val Leu Leu Ser Phe Pro Phe Ile
1 5 10 15

Phe

<210> 298
<211> 15
<212> PRT
<213> Homo sapiens

<400> 298
Gly His Phe Leu Asn Asp Leu Cys Ala Ser Met Trp Phe Thr Tyr
1 5 10 15

<210> 299
<211> 40

<212> PRT
<213> Homo sapiens

<400> 299
Ala Ile Pro Leu Arg Val Leu Val Val Leu Trp Ala Phe Val Leu Gly
1 5 10 15

Leu Ser Arg Val Met Leu Gly Arg His Asn Val Thr Asp Val Ala Phe
20 25 30

Gly Phe Phe Leu Gly Tyr Met Gln
35 40

<210> 300
<211> 13
<212> PRT
<213> Homo sapiens

<400> 300
Val Gly Leu Ser Arg Val Leu Gly Arg His Thr Asp Val
1 5 10

<210> 301
<211> 17
<212> PRT
<213> Homo sapiens

<400> 301
Ser Phe Tyr Lys Met Lys Arg Asn Ser Tyr Asp Arg Leu Arg Lys Val
1 5 10 15

Val

<210> 302
<211> 39
<212> PRT
<213> Homo sapiens

<400> 302
Leu His Gln Leu Arg Pro Pro His Arg Phe Pro Leu Ile Pro Pro Ala
1 5 10 15

Ala Ala Glu Gly Ala Gly Ala Pro Pro Gly Cys Gly Tyr Cys Val Phe
20 25 30

Trp Leu Leu Asn Pro Leu Pro
35

<210> 303
<211> 72
<212> PRT
<213> Homo sapiens

<400> 303
Met Pro Trp Lys Arg Ala Val Val Leu Leu Met Leu Trp Phe Ile Gly
1 5 10 15

Gln Ala Met Trp Leu Ala Pro Ala Tyr Val Leu Glu Phe Gln Gly Lys

20 25 30

Asn Thr Phe Leu Phe Ile Trp Leu Ala Gly Leu Phe Phe Leu Leu Ile
35 40 45

Asn Cys Ser Ile Leu Ile Gln Ile Ile Ser His Tyr Lys Glu Glu Pro
50 55 60

Leu Thr Glu Arg Ile Lys Tyr Asp
65 70

<210> 304
<211> 22
<212> PRT
<213> Homo sapiens

<400> 304
Ala Arg Ala Gln Pro Phe Ala Phe Gln Leu Arg Pro Ala Pro Gly Arg
1 5 10 15

Pro Gly Ser Pro Val Ala
20

<210> 305
<211> 297
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (12)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (50)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (79)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (297)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 305
Ala Gly Leu Pro Gly Ala Leu Thr Ala Pro Ala Xaa His His His Ala
1 5 10 15

Asp Ser Arg Pro Ala Glu Leu Val Val Gln Pro Leu Ser Pro Pro Arg
20 25 30

Pro Leu Leu Ser His Ala Gly Leu Ala Ser Ala Ala Gly Ala Ser Ser
35 40 45

Leu Xaa Arg Val Pro Gly Glu Ala Glu Ser Leu Cys Ala Leu Ser Pro

50 55 60

Gly Ser Ala Leu Arg Phe Pro Ala Ala Ser Cys Ser Arg Pro Xaa Arg
65 70 75 80

Glu Pro Ser Gly Asp Glu Gly Thr Ala Gly Ala Leu Pro Ser Pro Trp
85 90 95

Leu Ala Ala Leu Gly Pro Gly Gly Arg Pro Ala Val Arg Arg Val Leu
100 105 110

Pro Arg Leu Gly Gly Arg Ala Gly Gln Leu Pro Arg Gly Leu Pro Val
115 120 125

Pro Arg Gly Leu Arg His Ala Gly Arg Tyr His Leu Leu Arg Leu Leu
130 135 140

Arg Ala Pro Leu Leu Leu Arg Arg Gly Arg Arg Gln Ala Gly Ala Gly
145 150 155 160

Arg Leu His Gln Arg Pro Pro Arg Thr Gly Ala Pro Arg His His Cys
165 170 175

Ala Ala Cys Leu Arg Pro Leu Ser His Arg Arg Leu His Leu His Cys
180 185 190

Val His His Pro Gly Leu Cys Ser Gly Tyr Leu Leu Leu His Leu Phe
195 200 205

Glu Thr Gln Gly Ala Leu Ala Ala Ala Asn Pro Leu Leu Thr Pro Gln
210 215 220

Leu Ser Asp Arg Asp Pro Ala His Asp Pro Asp Leu His Gln Pro Gln
225 230 235 240

Gly Thr Leu Pro Ala Val Gln His Ser His Glu Leu Gln Leu His Arg
245 250 255

Arg Leu His Pro Gln Val Leu Leu Ser His Leu Val Ser Trp Cys His
260 265 270

Pro Ser Ile Ser Leu Thr Pro Phe Ser Arg Ser Pro His Trp Leu Gly
275 280 285

Arg Ala Val Gln Thr Phe Ser Ser Xaa
290 295

<210> 306
<211> 38
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (12)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 306
Ala Gly Leu Pro Gly Ala Leu Thr Ala Pro Ala Xaa His His His Ala

175

1 5 10 15

Asp Ser Arg Pro Ala Glu Leu Val Val Gln Pro Leu Ser Pro Pro Arg
20 25 30

Pro Leu Leu Ser His Ala
35

<210> 307
<211> 40
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (12)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 307
Gly Leu Ala Ser Ala Ala Gly Ala Ser Ser Leu Xaa Arg Val Pro Gly
1 5 10 15

Glu Ala Glu Ser Leu Cys Ala Leu Ser Pro Gly Ser Ala Leu Arg Phe
20 25 30

Pro Ala Ala Ser Cys Ser Arg Pro
35 40

<210> 308
<211> 40
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (1)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 308
Xaa Arg Glu Pro Ser Gly Asp Glu Gly Thr Ala Gly Ala Leu Pro Ser
1 5 10 15

Pro Trp Leu Ala Ala Leu Gly Pro Gly Gly Arg Pro Ala Val Arg Arg
20 25 30

Val Leu Pro Arg Leu Gly Gly Arg
35 40

<210> 309
<211> 40
<212> PRT
<213> Homo sapiens

<400> 309
Ala Gly Gln Leu Pro Arg Gly Leu Pro Val Pro Arg Gly Leu Arg His
1 5 10 15

Ala Gly Arg Tyr His Leu Leu Arg Leu Leu Arg Ala Pro Leu Leu Leu
20 25 30

Arg Arg Gly Arg Arg Gln Ala Gly
35 40

<210> 310
<211> 40
<212> PRT
<213> Homo sapiens

<400> 310
Ala Gly Arg Leu His Gln Arg Pro Pro Arg Thr Gly Ala Pro Arg His
1 5 10 15

His Cys Ala Ala Cys Leu Arg Pro Leu Ser His Arg Arg Leu His Leu
20 25 30

His Cys Val His His Pro Gly Leu
35 40

<210> 311
<211> 40
<212> PRT
<213> Homo sapiens

<400> 311
Cys Ser Gly Tyr Leu Leu Leu His Leu Phe Glu Thr Gln Gly Ala Leu
1 5 10 15

Ala Ala Ala Asn Pro Leu Leu Thr Pro Gln Leu Ser Asp Arg Asp Pro
20 25 30

Ala His Asp Pro Asp Leu His Gln
35 40

<210> 312
<211> 59
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (59)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 312
Pro Gln Gly Thr Leu Pro Ala Val Gln His Ser His Glu Leu Gln Leu
1 5 10 15

His Arg Arg Leu His Pro Gln Val Leu Leu Ser His Leu Val Ser Trp
20 25 30

Cys His Pro Ser Ile Ser Leu Thr Pro Phe Ser Arg Ser Pro His Trp
35 40 45

Leu Gly Arg Ala Val Gln Thr Phe Ser Ser Xaa
50 55

<210> 313
<211> 28

<212> PRT
<213> Homo sapiens

<400> 313
Val Ala His Thr Cys Asn Leu Ser Thr Leu Gly Gly Gln Gly Gly Arg
1 5 10 15

Ile Glu Arg Thr Ala Gly Gln Glu Phe Lys Thr Ser
20 25

<210> 314
<211> 19
<212> PRT
<213> Homo sapiens

<400> 314
Thr Ile Lys Met Gln Thr Glu Asn Leu Gly Val Val Tyr Tyr Val Asn
1 5 10 15

Lys Asp Phe

<210> 315
<211> 13
<212> PRT
<213> Homo sapiens

<400> 315
Val Glu Glu Asp Tyr Val Thr Asn Ile Arg Asn Asn Cys
1 5 10

<210> 316
<211> 7
<212> PRT
<213> Homo sapiens

<400> 316
Met Val Ser Asn Pro Pro Tyr
1 5

<210> 317
<211> 5
<212> PRT
<213> Homo sapiens

<400> 317
His Ala Ser Glu Leu
1 5

<210> 318
<211> 35
<212> PRT
<213> Homo sapiens

<400> 318
Leu Val Ala Leu Asp Arg Met Glu Tyr Val Arg Thr Phe Arg Lys Arg
1 5 10 15

Glu Asp Leu Arg Gly Arg Leu Phe Trp Val Ala Leu Asp Leu Leu Asp

20 25 30

Leu Leu Asp
35

<210> 319
<211> 88
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (21)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 319
Ser Val Ala Leu Phe Tyr Asn Phe Gly Lys Ser Trp Lys Ser Asp Pro
1 5 10 15

Gly Ile Ile Lys Xaa Thr Glu Glu Gln Lys Lys Lys Thr Ile Val Glu
20 25 30

Leu Ala Glu Thr Gly Ser Leu Asp Leu Ser Ile Phe Cys Ser Thr Cys
35 40 45

Leu Ile Arg Lys Pro Val Arg Ser Lys His Cys Gly Val Cys Asn Arg
50 55 60

Cys Ile Ala Lys Phe Asp His His Cys Pro Trp Val Gly Asn Cys Val
65 70 75 80

Gly Ala Gly Asn His Arg Tyr Phe
85

<210> 320
<211> 12
<212> PRT
<213> Homo sapiens

<400> 320
Phe Asp His His Cys Pro Trp Val Gly Asn Cys Val
1 5 10

<210> 321
<211> 20
<212> PRT
<213> Homo sapiens

<400> 321
Gln Met Tyr Gln Ile Ser Cys Leu Gly Ile Thr Thr Asn Glu Arg Met
1 5 10 15

Asn Ala Arg Arg
20

<210> 322
<211> 12
<212> PRT
<213> Homo sapiens

<400> 322
Arg Val Thr Ser Ser Leu Ala Met Leu Ser Asp Ser
1 5 10

<210> 323
<211> 15
<212> PRT
<213> Homo sapiens

<400> 323
Ala Ile Glu Arg Phe Ile Glu Pro His Glu Met Gln Gln Pro Leu
1 5 10 15

<210> 324
<211> 49
<212> PRT
<213> Homo sapiens

<400> 324
Asn Ala Leu Val Phe Tyr Phe Ser Trp Lys Gly Cys Ser Glu Gly Asp
1 5 10 15

Phe Cys Val Asn Pro Cys Phe Pro Asp Pro Cys Lys Pro Phe Val Glu
20 25 30

Ile Ile Asn Ser Thr His Ala Ser Val Tyr Glu Ala Gly Pro Cys Trp
35 40 45

Val

<210> 325
<211> 307
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (148)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 325
Ala Gly Ile Arg His Glu Arg Asn Arg Gly Arg Leu Leu Cys Met Leu
1 5 10 15

Ala Leu Thr Phe Met Phe Met Val Leu Glu Val Val Val Ser Arg Val
20 25 30

Thr Ser Ser Leu Ala Met Leu Ser Asp Ser Phe His Met Leu Ser Asp
35 40 45

Val Leu Ala Leu Val Val Ala Leu Val Ala Glu Arg Phe Ala Arg Arg
50 55 60

Thr His Ala Thr Gln Lys Asn Thr Phe Gly Trp Ile Arg Ala Glu Val
65 70 75 80

Met Gly Ala Leu Val Asn Ala Ile Phe Leu Thr Gly Leu Cys Phe Ala

180
85 90 95

Ile Leu Leu Glu Ala Ile Glu Arg Phe Ile Glu Pro His Glu Met Gln
100 105 110

Gln Pro Leu Val Val Leu Gly Val Gly Val Ala Gly Leu Leu Val Asn
115 120 125

Val Leu Gly Leu Cys Leu Phe His His His Ser Gly Phe Ser Gln Asp
130 135 140

Ser Gly His Xaa His Ser His Gly Gly His Gly His Gly His Gly Leu
145 150 155 160

Pro Lys Gly Pro Arg Val Lys Ser Thr Arg Pro Gly Ser Ser Asp Ile
165 170 175

Asn Val Ala Pro Gly Glu Gln Gly Pro Asp Gln Glu Glu Thr Asn Thr
180 185 190

Leu Val Ala Asn Thr Ser Asn Ser Asn Gly Leu Lys Leu Asp Pro Ala
195 200 205

Asp Pro Glu Asn Pro Arg Ser Gly Asp Thr Val Glu Val Gln Val Asn
210 215 220

Gly Asn Leu Val Arg Glu Pro Asp His Met Glu Leu Glu Glu Asp Arg
225 230 235 240

Ala Gly Gln Leu Asn Met Arg Gly Val Phe Leu His Val Leu Gly Asp
245 250 255

Ala Leu Gly Ser Val Ile Val Val Val Asn Ala Leu Val Phe Tyr Phe
260 265 270

Ser Trp Lys Gly Cys Ser Glu Gly Asp Phe Cys Val Asn Pro Cys Phe
275 280 285

Pro Asp Pro Cys Lys Ala Phe Val Glu Ile Leu Ile Val Leu Met His
290 295 300

Gln Phe Met
305

<210> 326
<211> 254
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (130)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 326
Met Phe Thr Phe Ala Ser Met Thr Lys Glu Asp Ser Lys Leu Ile Ala
1 5 10 15

Leu Ile Trp Pro Ser Glu Trp Gln Met Ile Gln Lys Leu Phe Val Val

20 25 30

Asp His Val Ile Lys Ile Thr Arg Ile Glu Val Gly Asp Val Asn Pro
35 40 45

Ser Glu Thr Gln Tyr Ile Ser Glu Pro Lys Leu Cys Pro Glu Cys Arg
50 55 60

Glu Gly Leu Leu Cys Gln Gln Gln Arg Asp Leu Arg Glu Tyr Thr Gln
65 70 75 80

Ala Thr Ile Tyr Val His Lys Val Val Asp Asn Lys Lys Val Met Lys
85 90 95

Asp Ser Ala Pro Glu Leu Asn Val Ser Ser Ser Glu Thr Glu Glu Asp
100 105 110

Lys Glu Glu Ala Lys Pro Asp Gly Glu Lys Asp Pro Asp Phe Asn Gln
115 120 125

Ser Xaa Gly Gly Thr Lys Arg Gln Lys Ile Ser His Gln Asn Tyr Ile
130 135 140

Ala Tyr Gln Lys Gln Val Ile Arg Arg Ser Met Arg His Arg Lys Val
145 150 155 160

Arg Gly Glu Lys Ala Leu Leu Val Ser Ala Asn Gln Thr Leu Lys Glu
165 170 175

Leu Lys Ile Gln Ile Met His Ala Phe Ser Val Ala Pro Phe Asp Gln
180 185 190

Asn Leu Ser Ile Asp Gly Lys Ile Leu Ser Asp Asp Cys Ala Thr Leu
195 200 205

Gly Thr Leu Gly Val Ile Pro Glu Ser Val Ile Leu Leu Lys Ala Asp
210 215 220

Glu Pro Ile Ala Asp Tyr Ala Ala Met Asp Asp Val Met Gln Val Cys
225 230 235 240

Met Pro Glu Glu Gly Phe Lys Gly Thr Gly Leu Leu Gly His
245 250

<210> 327
<211> 21
<212> PRT
<213> Homo sapiens

<400> 327
Ser Ala Pro Glu Leu Asn Val Ser Ser Ser Glu Thr Glu Glu Asp Lys
1 5 10 15

Glu Glu Ala Lys Pro
20

<210> 328
<211> 18
<212> PRT

<213> Homo sapiens

<400> 328
Lys Glu Leu Lys Ile Gln Ile Met His Ala Phe Ser Val Ala Pro Phe
1 5 10 15

Asp Gln

<210> 329
<211> 58
<212> PRT
<213> Homo sapiens

<400> 329
Phe Gln Asp Lys Asn Arg Pro Cys Leu Ser Asn Trp Pro Glu Asp Thr
1 5 10 15

Asp Val Leu Tyr Ile Val Ser Gln Phe Phe Val Glu Glu Trp Arg Lys
20 25 30

Phe Val Arg Lys Pro Thr Arg Cys Ser Pro Val Ser Ser Val Gly Asn
35 40 45

Ser Ala Leu Leu Cys Pro His Gly Gly Leu
50 55

<210> 330
<211> 42
<212> PRT
<213> Homo sapiens

<400> 330
Met Phe Thr Phe Ala Ser Met Thr Lys Glu Asp Ser Lys Leu Ile Ala
1 5 10 15

Leu Ile Trp Pro Ser Glu Trp Gln Met Ile Gln Lys Leu Phe Val Val
20 25 30

Asp His Val Ile Lys Ile Thr Arg Ile Glu
35 40

<210> 331
<211> 42
<212> PRT
<213> Homo sapiens

<400> 331
Val Gly Asp Val Asn Pro Ser Glu Thr Gln Tyr Ile Ser Glu Pro Lys
1 5 10 15

Leu Cys Pro Glu Cys Arg Glu Gly Leu Leu Cys Gln Gln Gln Arg Asp
20 25 30

Leu Arg Glu Tyr Thr Gln Ala Thr Ile Tyr
35 40

<210> 332
<211> 42

<212> PRT
<213> Homo sapiens

<400> 332
Val His Lys Val Val Asp Asn Lys Lys Val Met Lys Asp Ser Ala Pro
1 5 10 15

Glu Leu Asn Val Ser Ser Ser Glu Thr Glu Glu Asp Lys Glu Glu Ala
20 25 30

Lys Pro Asp Gly Glu Lys Asp Pro Asp Phe
35 40

<210> 333
<211> 42
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (4)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 333
Asn Gln Ser Xaa Gly Gly Thr Lys Arg Gln Lys Ile Ser His Gln Asn
1 5 10 15

Tyr Ile Ala Tyr Gln Lys Gln Val Ile Arg Arg Ser Met Arg His Arg
20 25 30

Lys Val Arg Gly Glu Lys Ala Leu Leu Val
35 40

<210> 334
<211> 42
<212> PRT
<213> Homo sapiens

<400> 334
Ser Ala Asn Gln Thr Leu Lys Glu Leu Lys Ile Gln Ile Met His Ala
1 5 10 15

Phe Ser Val Ala Pro Phe Asp Gln Asn Leu Ser Ile Asp Gly Lys Ile
20 25 30

Leu Ser Asp Asp Cys Ala Thr Leu Gly Thr
35 40

<210> 335
<211> 44
<212> PRT
<213> Homo sapiens

<400> 335
Leu Gly Val Ile Pro Glu Ser Val Ile Leu Leu Lys Ala Asp Glu Pro
1 5 10 15

Ile Ala Asp Tyr Ala Ala Met Asp Asp Val Met Gln Val Cys Met Pro
20 25 30

Glu Glu Gly Phe Lys Gly Thr Gly Leu Leu Gly His
35 40

<210> 336
<211> 18
<212> PRT
<213> Homo sapiens

<400> 336
Arg Gly Glu Arg Ser Glu Glu Leu Leu Gly Arg Glu Gly Leu Ser Gly
1 5 10 15

Ser Gln

<210> 337
<211> 179
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (119)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (123)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (177)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 337
Ala Glu Ala Ala Glu Gly Glu Lys Gly Val Arg Ser Cys Trp Ala Glu
1 5 10 15

Arg Asp Cys Pro Ala Pro Arg Cys Trp Ala Ser Trp Gly Ala Gln Pro
20 25 30

Ser Trp Asp Gly Ser Gln Val Leu Leu Trp Arg Ser Cys Cys Cys Cys
35 40 45

Cys Cys Trp Pro Pro Ala Phe Ser Thr Asp Gly Arg Thr Val Thr Trp
50 55 60

Arg Gly Thr Val Gln Leu Gln Gly Glu Thr Glu Ser Ala Gly Pro Ser
65 70 75 80

Leu Gly Pro Ser Gly Gly Gly Ala Thr Trp Glu Ser Phe Thr Ile Thr
85 90 95

Val Ile Leu Ala Thr Tyr Leu Met Cys Arg Met Trp Ala Ser Thr Thr
100 105 110

Thr Thr Thr Pro Ala Thr Xaa Leu Thr Thr Xaa Thr Thr Thr Thr Thr

185

115 120 125

Pro Thr Ala Thr Ile Pro Ala Thr Leu Ala Glu Ala Ala Val Ala Gly
130 135 140

Ala Cys Gly Gln Gln Leu Pro Leu Pro Ser His Leu Phe Pro Gly Gln
145 150 155 160

Val Asp Pro Met Phe Pro Cys Gly Arg Met His Leu Trp Gly Glu Arg
165 170 175

Xaa Glu Gln

<210> 338
<211> 12
<212> PRT
<213> Homo sapiens

<400> 338
Phe His Gly Leu Gly Arg Leu His Thr Val His Leu
1 5 10

<210> 339
<211> 21
<212> PRT
<213> Homo sapiens

<400> 339
Ala Ala Phe Thr Gly Leu Ala Leu Leu Glu Gln Leu Asp Leu Ser Asp
1 5 10 15

Asn Ala Gln Leu Arg
20

<210> 340
<211> 9
<212> PRT
<213> Homo sapiens

<400> 340
Ala Phe Arg Gly Leu His Ser Leu Asp
1 5

<210> 341
<211> 13
<212> PRT
<213> Homo sapiens

<400> 341
His Glu Val Pro Asp Ala Pro Arg Pro Thr Pro Thr Xaa
1 5 10

<210> 342
<211> 101
<212> PRT
<213> Homo sapiens

<400> 342

Met Val Val Ala Asp Arg Asn Arg Ala Ser Ser Ser Ser Tyr Leu Cys
1 5 10 15

Leu Leu Leu Phe Ser Leu Ser Leu Phe Leu Cys His Glu Thr Val Cys
20 25 30

Asp Arg Ala Thr Cys Leu Phe Phe Phe Leu Lys Phe Phe Phe Leu Phe
35 40 45

Met Cys Arg Cys Met Ser Trp Gly Phe Lys Asn Phe Lys Ala Gly Leu
50 55 60

Leu Met Gln Ser Met Pro Thr Ser Gly Ile Leu Arg Glu Arg Lys Arg
65 70 75 80

Leu His Val Val Arg Ile Pro Gln Gly Thr Glu Lys Lys Leu Glu Thr
85 90 95

Val Glu Met Gln Ile
100

<210> 343
<211> 12
<212> PRT
<213> Homo sapiens

<400> 343
Ile Pro Gln Gly Thr Glu Lys Lys Leu Glu Thr Val
1 5 10

<210> 344
<211> 37
<212> PRT
<213> Homo sapiens

<400> 344
Asn Pro Arg Leu Pro Leu Pro Arg Gly Gly Ser Leu Arg Leu Leu Ser
1 5 10 15

Ser Pro Ala Asn Ser Asn Asn Ala Lys Ala Tyr Pro Phe Ser Arg Phe
20 25 30

Pro Ser Pro Ile Phe
35

<210> 345
<211> 48
<212> PRT
<213> Homo sapiens

<400> 345
Met Val Gln Glu Ala Pro Ala Leu Val Arg Leu Ser Leu Gly Ser His
1 5 10 15

Arg Val Lys Gly Pro Leu Pro Val Leu Lys Leu Gln Pro Glu Gly Trp
20 25 30

Ser Pro Ser Thr Leu Trp Ser Cys Ala Ser Val Trp Lys Asp Ser Cys
35 40 45

<210> 346
<211> 122
<212> PRT
<213> Homo sapiens

<400> 346
Ala Leu Ala Ser Ser Leu Val Ala Glu Asn Gln Gly Phe Val Ala Ala
1 5 10 15

Leu Met Val Gln Glu Ala Pro Ala Leu Val Arg Leu Ser Leu Gly Ser
20 25 30

His Arg Val Lys Gly Pro Leu Pro Val Leu Lys Leu Gln Pro Glu Gly
35 40 45

Trp Ser Pro Ser Thr Leu Trp Ser Cys Ala Ser Val Trp Lys Asp Ser
50 55 60

Cys Met His Pro Trp Arg Leu Ser Met Cys Pro Ala Cys Val Leu Ala
65 70 75 80

Ala Leu Pro Ala Leu Cys Ser Cys Leu Cys Ser Pro Asp Ala Arg Pro
85 90 95

Pro His Gly Trp Met Ser Met Pro Phe Thr Pro His Pro Leu Val Ser
100 105 110

Arg Ala Met Pro Thr Cys His Pro Cys Ser
115 120

<210> 347
<211> 33
<212> PRT
<213> Homo sapiens

<400> 347
Phe Tyr Phe Ile Thr Leu Ile Phe Phe Leu Ala Trp Leu Val Lys Asn
1 5 10 15

Val Phe Ile Ala Val Ile Ile Glu Thr Phe Ala Glu Ile Arg Val Gln
20 25 30

Phe

<210> 348
<211> 15
<212> PRT
<213> Homo sapiens

<400> 348
Ser Ile Phe Thr Val Tyr Glu Ala Ala Ser Gln Glu Gly Trp Val
1 5 10 15

<210> 349

<211> 21
<212> PRT
<213> Homo sapiens

<400> 349
His Glu Gly Thr Ser Ile Phe Thr Val Tyr Glu Ala Ala Ser Gln Glu
1 5 10 15

Gly Trp Val Phe Leu
20

<210> 350
<211> 8
<212> PRT
<213> Homo sapiens

<400> 350
Cys Lys Thr Ser Phe Gly Leu Ala
1 5

<210> 351
<211> 122
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (73)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 351
Met Ile Thr Leu Ser Ser Ala Phe Ser Ala Lys Gln Lys Thr His Ala
1 5 10 15

His Lys Asn Thr His Ala Cys Met Cys Ala Thr Asp Met Ala Asn Pro
20 25 30

Lys Leu Val Leu His Phe Glu Val Ile Val Ala Leu Leu Ser Leu Leu
35 40 45

Gln Thr Ile Leu Ser Leu Leu Leu Gly Gln Arg Thr Trp Leu Ala His
50 55 60

Leu Tyr Val Leu Ser Thr Glu Asn Xaa Ala Leu His Thr Val Gly Thr
65 70 75 80

Gln Lys His Leu Leu Pro His Asp Trp Cys Phe Gly Lys His Cys Val
85 90 95

Ser Cys Arg His His Ile Phe His Arg Phe Cys Ser Ile Phe Ser Ser
100 105 110

Thr Leu Lys Arg Ser Gln Gly Phe Glu Gly
115 120

<210> 352
<211> 13
<212> PRT
<213> Homo sapiens

<400> 352
Cys Ala Ala Pro Gly Asn Lys Thr Ser His Leu Ala Ala
1 5 10

<210> 353
<211> 24
<212> PRT
<213> Homo sapiens

<400> 353
Glu His Pro Leu Tyr Arg Ala Gly His Leu Ile Leu Gln Asp Arg Ala
1 5 10 15

Ser Cys Leu Pro Ala Met Leu Leu
20

<210> 354
<211> 15
<212> PRT
<213> Homo sapiens

<400> 354
Leu Leu Asp Pro Ser Cys Ser Gly Ser Gly Met Pro Ser Arg Gln
1 5 10 15

<210> 355
<211> 23
<212> PRT
<213> Homo sapiens

<400> 355
Tyr Ser Thr Cys Ser Leu Cys Gln Glu Glu Asn Glu Asp Val Val Arg
1 5 10 15

Asp Ala Leu Gln Gln Asn Pro
20

<210> 356
<211> 470
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (277)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (296)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (301)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE
<222> (306)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (324)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (431)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 356

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Ser Ala Thr Glu His Gly Ala Val Cys Cys Ser Cys Arg Arg Val Gly
  1               5                  10                  15

Arg Arg Gly Glu Pro Pro Gly Ser Ile Lys Gly Leu Val Tyr Ser Ser
             20                  25                  30

Asn Phe Gln Asn Val Lys Gln Leu Tyr Ala Leu Val Cys Glu Thr Gln
         35                  40                  45

Arg Tyr Ser Ala Val Leu Asp Ala Val Ile Ala Ser Ala Gly Leu Leu
     50                  55                  60

Arg Ala Glu Lys Lys Leu Arg Pro His Leu Ala Lys Val Leu Val Tyr
 65                  70                  75                  80

Glu Leu Leu Leu Gly Lys Gly Phe Arg Gly Gly Gly Gly Arg Trp Lys
                 85                  90                  95

Ala Leu Leu Gly Arg His Gln Ala Arg Leu Lys Ala Glu Leu Ala Arg
            100                 105                 110

Leu Lys Val His Arg Gly Val Ser Arg Asn Glu Asp Leu Leu Glu Val
        115                 120                 125

Gly Ser Arg Pro Gly Pro Ala Ser Gln Leu Pro Arg Phe Val Arg Val
    130                 135                 140

Asn Thr Leu Lys Thr Cys Ser Asp Asp Val Val Asp Tyr Phe Lys Arg
145                 150                 155                 160

Gln Gly Phe Ser Tyr Gln Gly Arg Ala Ser Ser Leu Asp Asp Leu Arg
                165                 170                 175

Ala Leu Lys Gly Lys His Phe Leu Leu Asp Pro Leu Met Pro Glu Leu
            180                 185                 190

Leu Val Phe Pro Ala Gln Thr Asp Leu His Glu His Pro Leu Tyr Arg
        195                 200                 205

Ala Gly His Leu Ile Leu Gln Asp Arg Ala Ser Cys Leu Pro Ala Met
    210                 215                 220

Leu Leu Asp Pro Pro Pro Gly Ser His Val Ile Asp Ala Cys Ala Ala
225                 230                 235                 240
```

```
Pro Gly Asn Lys Thr Ser His Leu Ala Ala Leu Leu Lys Asn Gln Gly
                245                 250                 255

Lys Ile Phe Ala Phe Asp Leu Asp Ala Lys Arg Leu Ala Ser Met Ala
            260                 265                 270

Thr Leu Leu Ala Xaa Ala Gly Val Ser Cys Cys Glu Leu Ala Glu Glu
        275                 280                 285

Asp Phe Leu Ala Val Ser Pro Xaa Asp Pro Arg Tyr Xaa Glu Val His
    290                 295                 300

Tyr Xaa Leu Leu Asp Pro Ser Cys Ser Gly Ser Gly Met Pro Ser Arg
305                 310                 315                 320

Gln Leu Glu Xaa Pro Gly Ala Gly Thr Pro Ser Pro Val Arg Leu His
                325                 330                 335

Ala Leu Ala Gly Phe Gln Gln Arg Ala Leu Cys His Ala Leu Thr Phe
            340                 345                 350

Pro Ser Leu Gln Arg Leu Val Tyr Ser Thr Cys Ser Leu Cys Gln Glu
        355                 360                 365

Glu Asn Glu Asp Val Val Arg Asp Ala Leu Gln Gln Asn Pro Gly Ala
    370                 375                 380

Phe Arg Leu Ala Pro Ala Leu Pro Ala Trp Pro His Arg Gly Leu Ser
385                 390                 395                 400

Thr Phe Pro Gly Ala Glu His Cys Leu Arg Ala Ser Pro Glu Thr Thr
                405                 410                 415

Leu Ser Ser Gly Phe Phe Val Ala Val Ile Glu Arg Val Glu Xaa Pro
            420                 425                 430

Ser Ser Ala Ser Gln Ala Lys Ala Ser Ala Pro Glu Arg Thr Pro Ser
        435                 440                 445

Pro Ala Pro Lys Arg Lys Lys Arg Gln Gln Arg Ala Ala Ala Gly Ala
    450                 455                 460

Cys Thr Pro Pro Cys Thr
465                 470

<210> 357
<211> 429
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (236)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (255)
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<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (260)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (265)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (418)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 357

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Tyr Glu Pro His Ser Thr His Ser Arg Glu Arg Ala Met Thr Ser His
  1               5                  10                  15

Ala Arg Val Ser Leu Gly Pro Ser Arg Asp Pro Leu Glu Arg Pro His
             20                  25                  30

Leu Ala Lys Val Leu Val Tyr Glu Leu Leu Leu Gly Lys Gly Phe Arg
         35                  40                  45

Gly Gly Gly Gly Arg Trp Lys Ala Leu Leu Gly Arg His Gln Ala Arg
     50                  55                  60

Leu Lys Ala Glu Leu Ala Arg Leu Lys Val His Arg Gly Val Ser Arg
 65                  70                  75                  80

Asn Glu Asp Leu Leu Glu Val Gly Ser Arg Pro Gly Pro Ala Ser Gln
                 85                  90                  95

Leu Pro Arg Phe Val Arg Val Asn Thr Leu Lys Thr Cys Ser Asp Asp
            100                 105                 110

Val Val Asp Tyr Phe Lys Arg Gln Gly Phe Ser Tyr Gln Gly Arg Ala
        115                 120                 125

Ser Ser Leu Asp Asp Leu Arg Ala Leu Lys Gly Lys His Phe Leu Leu
    130                 135                 140

Asp Pro Leu Met Pro Glu Leu Leu Val Phe Pro Ala Gln Thr Asp Leu
145                 150                 155                 160

His Glu His Pro Leu Tyr Arg Ala Gly His Leu Ile Leu Gln Asp Arg
                165                 170                 175

Ala Ser Cys Leu Pro Ala Met Leu Leu Asp Pro Pro Pro Gly Ser His
            180                 185                 190

Val Ile Asp Ala Cys Ala Ala Pro Gly Asn Lys Thr Ser His Leu Ala
        195                 200                 205

Ala Leu Leu Lys Asn Gln Gly Lys Ile Phe Ala Phe Asp Leu Asp Ala
    210                 215                 220
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```
Lys Arg Leu Ala Ser Met Ala Thr Leu Leu Ala Xaa Ala Gly Val Ser
225                 230                 235                 240

Cys Cys Glu Leu Ala Glu Glu Asp Phe Leu Ala Val Ser Pro Xaa Asp
                245                 250                 255

Pro Arg Tyr Xaa Glu Val His Tyr Xaa Leu Leu Asp Pro Ser Cys Ser
            260                 265                 270

Gly Ser Gly Met Pro Ser Arg Gln Leu Glu Glu Pro Gly Ala Gly Thr
        275                 280                 285

Pro Ser Pro Val Arg Leu His Ala Leu Ala Gly Phe Gln Gln Arg Ala
    290                 295                 300

Leu Cys His Ala Leu Thr Phe Pro Ser Leu Gln Arg Leu Val Tyr Ser
305                 310                 315                 320

Thr Cys Ser Leu Cys Gln Glu Glu Asn Glu Asp Val Val Arg Asp Ala
                325                 330                 335

Leu Gln Gln Asn Pro Gly Ala Phe Arg Leu Ala Pro Ala Leu Pro Ala
            340                 345                 350

Trp Pro His Arg Gly Leu Ser Thr Phe Pro Gly Ala Glu His Cys Leu
        355                 360                 365

Arg Ala Ser Pro Glu Thr Thr Leu Ser Ser Gly Phe Phe Val Ala Val
    370                 375                 380

Ile Glu Arg Val Glu Val Pro Ser Ser Ala Ser Gln Ala Lys Ala Ser
385                 390                 395                 400

Ala Pro Glu Arg Thr Pro Ser Pro Ala Pro Lys Arg Lys Lys Arg Gln
                405                 410                 415

Gln Xaa Ala Ala Ala Gly Ala Cys Thr Pro Pro Cys Thr
            420                 425

<210> 358
<211> 245
<212> PRT
<213> Homo sapiens

<400> 358
Met Gly Thr His Ser Val Ser Gly Arg Phe Ser Lys Thr Ser Pro Pro
  1               5                  10                  15

Tyr Cys Pro Pro Ser Ser Ser Leu Pro Gly Pro Ile Ser Ser Ile Gly
             20                  25                  30

Phe Asn Lys Ser Leu His Glu Cys Leu Phe Ile Ser Glu Lys Glu Leu
         35                  40                  45

Leu Pro Leu Pro Phe Pro Phe Pro Asp Leu Lys Ser Phe Ile Ser Tyr
     50                  55                  60

Leu Thr Ser Met Leu Lys Pro Gly Pro Leu Ile Val Ser Leu Lys Ile
```

65 70 75 80

Trp Val Ser Tyr Pro Ile Thr Arg Pro Arg Tyr Leu Pro Pro Met Leu
85 90 95

Lys Ser Leu Asn Ile Ser Phe Leu Tyr Ile Gln Tyr Ile Trp Ala Tyr
100 105 110

Ile His Leu Tyr Thr Ser Phe Tyr Ile Tyr Ile Ile Ser Val Ser Phe
115 120 125

Phe Leu Asp Lys Pro Phe Ile Tyr Val Ile Ser Phe Pro Lys Pro Pro
130 135 140

His Phe Leu Phe Ala Ser Leu Ser Lys Thr Gln Glu Phe His Phe His
145 150 155 160

Val Pro Gln His His Phe Phe Leu Ile Phe Ser Pro Gln Val Ser Ser
165 170 175

Pro Ile Ser Cys Phe Ala Arg Leu Leu Lys Ser Pro Leu Phe Thr Pro
180 185 190

Val Pro Thr Glu Ile Ser Pro Phe Tyr Asn Cys Ala Tyr Tyr Ser Ala
195 200 205

Asp Ile Pro Ser Pro Gln Leu Val Trp Gly Pro Ile Ser His Gln Thr
210 215 220

Trp Leu Leu Leu Lys Leu Gly Leu Leu Pro Lys Arg Gly Phe Gln Val
225 230 235 240

Arg Gly Asp Arg Leu
245

<210> 359
<211> 29
<212> PRT
<213> Homo sapiens

<400> 359
Cys Phe Ala Arg Leu Leu Lys Ser Pro Leu Phe Thr Pro Val Pro Thr
1 5 10 15

Glu Ile Ser Pro Phe Tyr Asn Cys Ala Tyr Tyr Ser Ala
20 25

<210> 360
<211> 111
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (47)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 360
Asn Arg Glu Gln Lys Ala Lys Ser Gln Leu Leu Arg Ser Gln Leu Tyr

195

1 5 10 15

Ser Thr Leu Asp Leu Pro Tyr Phe Phe Gln Cys Val Gly Thr Arg Cys
20 25 30

Thr Ala Val Cys Val Cys Val Cys Val Cys Val Cys Val Cys Xaa Tyr
35 40 45

Leu Pro Ile His Trp Gln Val Asn Leu His Leu Val Tyr Leu Ala Met
50 55 60

Leu Cys Phe Leu Pro Ile Pro Leu Leu Ser Ile Leu Ser Pro Gln Thr
65 70 75 80

Gln Ala Ser Arg Leu Leu Asp Glu Thr Val Arg Arg Lys His Phe Leu
85 90 95

Thr Tyr Pro Phe Gly Ile Ser Ser Ile Ile Thr Gln Ala Leu Leu
100 105 110

<210> 361
<211> 51
<212> PRT
<213> Homo sapiens

<400> 361
Pro Gly Pro Glu Ala Gln Pro Trp Pro Gly Pro Asp Leu Pro Ala Val
1 5 10 15

Gly Ser Arg Gly Pro Gly Arg Leu Leu Ala Ala Val Ser Ala Pro Arg
20 25 30

Leu Gly Leu Gly Leu Ala Gly Ala Asp Pro Val Gly Pro Glu Ala Cys
35 40 45

His Leu Pro
50

<210> 362
<211> 42
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (32)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 362
Gly Arg Leu Arg Gly Pro Asp Glu Val Gly Ala Pro Phe His Pro Gly
1 5 10 15

Pro Ala Thr Pro Gly Leu Ala Asp Pro Leu Arg Pro Ala Glu Pro Xaa
20 25 30

His Trp Leu Pro Ser Leu Trp Gly Pro Thr
35 40

<210> 363

<211> 19
<212> PRT
<213> Homo sapiens

<400> 363
Pro Gly Pro Glu Ala Gln Pro Trp Pro Gly Pro Asp Leu Pro Ala Val
1 5 10 15

Gly Ser Arg

<210> 364
<211> 19
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (15)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 364
Ala Thr Pro Gly Leu Ala Asp Pro Leu Arg Pro Ala Glu Pro Xaa His
1 5 10 15

Trp Leu Pro

<210> 365
<211> 251
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (210)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (241)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 365
Gln Trp Pro Glu Lys Asp Pro Val Met Ala Ala Ser Ser Ile Ser Ser
1 5 10 15

Pro Trp Gly Lys His Val Phe Lys Ala Ile Leu Met Val Leu Val Ala
20 25 30

Leu Ile Leu Leu His Ser Ala Leu Ala Gln Ser Arg Arg Asp Phe Ala
35 40 45

Pro Pro Gly Gln Gln Lys Arg Glu Ala Pro Val Asp Val Leu Thr Gln
50 55 60

Ile Gly Arg Ser Val Arg Gly Thr Leu Asp Ala Trp Ile Gly Pro Glu
65 70 75 80

Thr Met His Leu Val Ser Glu Ser Ser Ser Gln Val Leu Trp Ala Ile
85 90 95

Ser Ser Ala Ile Ser Val Ala Phe Phe Ala Leu Ser Gly Ile Ala Ala
100 105 110

Gln Leu Leu Asn Ala Leu Gly Leu Ala Gly Asp Tyr Leu Ala Gln Gly
115 120 125

Leu Lys Leu Ser Pro Gly Gln Val Gln Thr Phe Leu Leu Trp Gly Ala
130 135 140

Gly Ala Leu Val Val Tyr Trp Leu Leu Ser Leu Leu Leu Gly Leu Val
145 150 155 160

Leu Ala Leu Leu Gly Arg Ile Leu Trp Gly Leu Lys Leu Val Ile Phe
165 170 175

Leu Ala Gly Phe Val Ala Leu Met Arg Ser Val Pro Asp Pro Ser Thr
180 185 190

Arg Ala Leu Leu Leu Leu Ala Leu Leu Ile Leu Tyr Ala Leu Leu Ser
195 200 205

Arg Xaa Thr Gly Ser Arg Ala Ser Gly Ala Gln Leu Glu Ala Lys Val
210 215 220

Arg Gly Leu Glu Arg Gln Val Glu Glu Leu Arg Trp Arg Gln Arg Gln
225 230 235 240

Xaa Ala Lys Gly Ala Arg Ser Val Glu Glu Glu
245 250

<210> 366
<211> 116
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (2)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (5)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (7)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (9)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 366

Glu Xaa Pro Arg Xaa Ile Xaa Gly Xaa Asn Ala Pro Gln Val Pro Val
1 5 10 15

Arg Asn Ser Arg Val Asp Pro Arg Val Arg Pro Arg Val Arg Ser Leu
20 25 30

Val Phe Val Leu Phe Cys Asp Glu Val Arg Gln Trp Tyr Val Asn Gly
35 40 45

Val Asn Tyr Phe Thr Asp Leu Trp Asn Val Met Asp Thr Leu Gly Leu
50 55 60

Phe Tyr Phe Ile Ala Gly Ile Val Phe Arg Leu His Ser Ser Asn Lys
65 70 75 80

Ser Ser Leu Tyr Ser Gly Arg Val Ile Phe Cys Leu Asp Tyr Ile Ile
85 90 95

Phe Thr Leu Arg Leu Ile His Ile Phe Thr Val Ser Arg Asn Leu Gly
100 105 110

Pro Lys Ile Ile
115

<210> 367
<211> 12
<212> PRT
<213> Homo sapiens

<400> 367
Asn Ile Leu Leu Val Asn Leu Leu Val Ala Met Phe
1 5 10

<210> 368
<211> 10
<212> PRT
<213> Homo sapiens

<400> 368
Gln Val Trp Lys Phe Gln Arg Tyr Phe Leu
1 5 10

<210> 369
<211> 316
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (2)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (5)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE

<222> (7)
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<220>
<221> SITE
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<220>
<221> SITE
<222> (126)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (127)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
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<222> (143)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
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<222> (166)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
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<222> (176)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (200)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
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<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (296)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (306)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 369
Glu Xaa Pro Arg Xaa Ile Xaa Gly Xaa Asn Ala Pro Gln Val Pro Val
1 5 10 15

Arg Asn Ser Arg Val Asp Pro Arg Val Arg Pro Arg Val Arg Ser Leu
20 25 30

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Val Phe Val Leu Phe Cys Asp Glu Val Arg Gln Trp Tyr Val Asn Gly
         35                  40                  45

Val Asn Tyr Phe Thr Asp Leu Trp Asn Val Met Asp Thr Leu Gly Leu
     50                  55                  60

Phe Tyr Phe Ile Ala Gly Ile Val Phe Arg Leu His Ser Ser Asn Lys
 65                  70                  75                  80

Ser Ser Leu Tyr Ser Gly Arg Val Ile Phe Cys Leu Asp Tyr Ile Ile
                 85                  90                  95

Phe Thr Leu Arg Leu Ile His Ile Phe Thr Val Ser Arg Asn Leu Gly
            100                 105                 110

Pro Lys Ile Ile Met Leu Gln Arg Met Leu Ile Asp Val Xaa Xaa Phe
        115                 120                 125

Leu Phe Leu Phe Ala Val Trp Met Val Ala Phe Gly Val Ala Xaa Gln
    130                 135                 140

Gly Ile Leu Arg Gln Asn Glu Gln Arg Trp Arg Trp Ile Phe Arg Ser
145                 150                 155                 160

Val Ile Tyr Glu Pro Xaa Leu Ala Met Phe Gly Gln Val Pro Ser Xaa
                165                 170                 175

Val Asp Gly Thr Thr Tyr Asp Phe Ala His Cys Thr Phe Thr Gly Asn
            180                 185                 190

Glu Ser Lys Pro Leu Cys Val Xaa Leu Asp Glu His Asn Leu Pro Arg
        195                 200                 205

Phe Pro Glu Trp Ile Thr Ile Pro Leu Val Cys Ile Tyr Met Leu Ser
    210                 215                 220

Thr Asn Ile Leu Leu Val Asn Leu Leu Val Ala Met Phe Gly Tyr Thr
225                 230                 235                 240

Val Gly Thr Val Gln Glu Asn Asn Asp Gln Val Trp Lys Phe Gln Arg
                245                 250                 255

Tyr Phe Leu Val Gln Glu Tyr Cys Ser Arg Leu Asn Ile Pro Phe Pro
            260                 265                 270

Phe Ile Val Phe Ala Tyr Phe Tyr Met Val Val Lys Lys Cys Phe Lys
        275                 280                 285

Cys Cys Cys Lys Glu Xaa Asn Xaa Glu Ser Ser Val Cys Cys Ser Lys
    290                 295                 300

Met Xaa Thr Met Arg Leu Trp His Gly Arg Val Ser
305                 310                 315
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<210> 370
<211> 129
<212> PRT
<213> Homo sapiens

<400> 370
Met Glu Phe Gln Asn Met Tyr Ile Gln Leu Phe Gly Phe Ser Phe Phe
1 5 10 15

Ile Val Ile Ile Val Arg Met Leu Leu Leu Gly Leu Cys Val Ser Ala
20 25 30

Arg Gln Pro Val Met Pro Arg Ala Thr Leu Trp Gly His Leu Ser Pro
35 40 45

Ala Trp Val Leu Val Pro Trp Thr Pro Arg Ala Cys Gly Gln Ala Ala
50 55 60

Pro Gly Arg Gly His Val Ala Ser Asp His Lys Ser Gly Leu Pro Trp
65 70 75 80

Pro Lys His Cys Ser Cys Leu His Pro Arg Ala Ser Gln Pro Cys Leu
85 90 95

Phe Ser Leu Asn Ser Asn Arg Thr Val Phe Thr Ala Ile Gln Arg Val
100 105 110

Ala Leu Gly Trp Thr Phe Trp Val Gln Ala Asn Leu Val Pro Arg Cys
115 120 125

Thr

<210> 371
<211> 417
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (54)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (90)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (109)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
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<223> Xaa equals any of the naturally occurring L-amino acids

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<223> Xaa equals any of the naturally occurring L-amino acids

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<222> (135)
<223> Xaa equals any of the naturally occurring L-amino acids

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<222> (137)
<223> Xaa equals any of the naturally occurring L-amino acids

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<222> (139)
<223> Xaa equals any of the naturally occurring L-amino acids

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<222> (188)
<223> Xaa equals any of the naturally occurring L-amino acids

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<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (223)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (249)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (252)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (322)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (348)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (402)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 371
Leu Leu Leu Cys Val Thr Gly Val Tyr Ser Tyr Gly Leu Met His Pro
1 5 10 15

Ile Pro Ser Ser Phe Met Ile Lys Ala Val Ser Ser Phe Leu Thr Ala
20 25 30

Glu Glu Ala Ser Val Gly Asn Pro Glu Gly Ala Phe Met Lys Val Leu
35 40 45

Gln Ala Arg Lys Asn Xaa Thr Ser Thr Glu Leu Ile Val Glu Pro Glu
50 55 60

Glu Pro Ser Asp Ser Ser Gly Ile Asn Leu Ser Gly Phe Gly Ser Glu
65 70 75 80

Gln Leu Asp Thr Asn Asp Glu Ser Asp Xaa Ile Ser Thr Leu Ser Tyr
85 90 95

Ile Leu Pro Tyr Phe Ser Ala Val Asn Leu Asp Val Xaa Ser Xaa Leu
100 105 110

Leu Pro Phe Ile Lys Leu Pro Thr Xaa Gly Asn Ser Leu Ala Lys Ile
115 120 125

Gln Thr Val Gly Gln Asn Xaa Gln Xaa Val Xaa Arg Val Leu Met Gly
130 135 140

Pro Arg Ser Ile Gln Lys Arg His Phe Lys Glu Val Gly Arg Gln Ser
145 150 155 160

Ile Arg Arg Glu Gln Gly Ala Gln Ala Ser Val Glu Asn Ala Ala Glu
165 170 175

Glu Lys Arg Leu Gly Ser Pro Ala Pro Arg Glu Xaa Glu Gln Pro His
180 185 190

Thr Gln Gln Gly Pro Glu Lys Leu Ala Gly Asn Ala Xaa Tyr Thr Lys
195 200 205

Pro Ser Phe Thr Gln Glu His Lys Ala Ala Val Ser Val Leu Xaa Pro
210 215 220

Phe Ser Lys Gly Ala Pro Ser Thr Ser Ser Pro Ala Lys Ala Leu Pro
225 230 235 240

Gln Val Arg Asp Arg Trp Lys Asp Xaa Thr His Xaa Ile Ser Ile Leu
245 250 255

Glu Ser Ala Lys Ala Arg Val Thr Asn Met Lys Ala Ser Lys Pro Ile
260 265 270

Ser His Ser Arg Lys Lys Tyr Arg Phe His Lys Thr Arg Ser Arg Met
275 280 285

Thr His Arg Thr Pro Lys Val Lys Lys Ser Pro Lys Phe Arg Lys Lys
290 295 300

Ser Tyr Leu Ser Arg Leu Met Leu Ala Asn Arg Pro Pro Phe Ser Ala
305 310 315 320

Ala Xaa Ser Leu Ile Asn Ser Pro Ser Gln Gly Ala Phe Ser Ser Leu
325 330 335

```
Gly Asp Leu Ser Pro Gln Glu Asn Pro Phe Leu Xaa Val Ser Ala Pro
            340                 345                 350

Ser Glu His Phe Ile Glu Thr Thr Asn Ile Lys Asp Thr Thr Ala Arg
        355                 360                 365

Asn Ala Leu Glu Glu Asn Val Phe Met Glu Asn Thr Asn Met Pro Glu
    370                 375                 380

Val Thr Ile Ser Glu Asn Thr Asn Tyr Asn His Pro Pro Glu Ala Asp
385                 390                 395                 400

Ser Xaa Gly Thr Ala Phe Asn Leu Gly Pro Thr Val Lys Gln Thr Glu
                405                 410                 415

Thr
```

<210> 372
<211> 94
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (66)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 372

```
Cys Phe Ser Asn Ala Pro Lys Val Ser Asp Glu Ala Val Lys Lys Asp
  1               5                  10                  15

Ser Glu Leu Asp Lys His Leu Glu Ser Arg Val Glu Glu Ile Met Glu
             20                  25                  30

Lys Ser Gly Glu Glu Gly Met Pro Asp Leu Ala His Val Met Arg Ile
         35                  40                  45

Leu Ser Ala Glu Asn Ile Pro Asn Leu Pro Pro Gly Gly Gly Leu Ala
     50                  55                  60

Gly Xaa Arg Asn Val Ile Glu Ala Val Tyr Ser Arg Leu Asn Pro His
 65                  70                  75                  80

Arg Glu Ser Asp Gly Gly Ala Gly Asp Leu Glu Asp Pro Trp
                85                  90
```

<210> 373
<211> 56
<212> PRT
<213> Homo sapiens

<400> 373

```
Cys Phe Ser Asn Ala Pro Lys Val Ser Asp Glu Ala Val Lys Lys Asp
  1               5                  10                  15

Ser Glu Leu Asp Lys His Leu Glu Ser Arg Val Glu Glu Ile Met Glu
             20                  25                  30
```

Lys Ser Gly Glu Glu Gly Met Pro Asp Leu Ala His Val Met Arg Ile
35 40 45

Leu Ser Ala Glu Asn Ile Pro Asn
50 55

<210> 374
<211> 26
<212> PRT
<213> Homo sapiens

<400> 374
Arg Asn Val Ile Glu Ala Val Tyr Ser Arg Leu Asn Pro His Arg Glu
1 5 10 15

Ser Asp Gly Gly Ala Gly Asp Leu Glu Asp
20 25

<210> 375
<211> 16
<212> PRT
<213> Homo sapiens

<400> 375
Asp Ser Glu Leu Asp Lys His Leu Glu Ser Arg Val Glu Glu Ile Met
1 5 10 15

<210> 376
<211> 24
<212> PRT
<213> Homo sapiens

<400> 376
Lys Ser Gly Glu Glu Gly Met Pro Asp Leu Ala His Val Met Arg Ile
1 5 10 15

Leu Ser Ala Glu Asn Ile Pro Asn
20

<210> 377
<211> 9
<212> PRT
<213> Homo sapiens

<400> 377
Cys Phe Ser Asn Ala Pro Lys Val Ser
1 5

<210> 378
<211> 69
<212> PRT
<213> Homo sapiens

<400> 378
Met Ser Arg Lys Ser Leu Ala Phe Pro Ile Ile Cys Ser Tyr Leu Cys

206

1 5 10 15

Phe Leu Thr Val Ala Thr Cys Ser Ile Ala Cys Thr Thr Val Phe Phe
20 25 30

Ala Asn Leu Arg His Thr Arg Tyr Ile Cys Ile Glu Leu Ser Ala Leu
35 40 45

Glu Thr Ser Gly Val Ile Ser Pro Gln Ile Asn Asn Val Pro Glu Val
50 55 60

His Gly Lys Tyr Ser
65

<210> 379
<211> 16
<212> PRT
<213> Homo sapiens

<400> 379
Ile Gln Lys Met Thr Arg Val Arg Val Val Asp Asn Ser Ala Leu Gly
1 5 10 15

<210> 380
<211> 14
<212> PRT
<213> Homo sapiens

<400> 380
Pro Arg Cys Ile His Val Tyr Lys Lys Asn Gly Val Gly Lys
1 5 10

<210> 381
<211> 15
<212> PRT
<213> Homo sapiens

<400> 381
Gly Asp Gln Ile Leu Leu Ala Ile Lys Gly Gln Lys Lys Lys Ala
1 5 10 15

<210> 382
<211> 15
<212> PRT
<213> Homo sapiens

<400> 382
Asn Pro Val Gly Thr Arg Ile Lys Thr Pro Ile Pro Thr Ser Leu
1 5 10 15

<210> 383
<211> 171
<212> PRT
<213> Homo sapiens

<220>

<221> SITE
<222> (20)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 383
Val Leu Ile Pro Ser Phe Ser Ser Ser Phe Leu Cys Ser Arg Gly Gly
1 5 10 15

Pro Leu Pro Xaa Asp Leu Ser Trp Asp Pro Met Ala Phe Phe Thr Gly
20 25 30

Leu Trp Gly Pro Phe Thr Cys Val Ser Arg Val Leu Ser His His Cys
35 40 45

Phe Ser Thr Thr Gly Ser Leu Ser Ala Ile Gln Lys Met Thr Arg Val
50 55 60

Arg Val Val Asp Asn Ser Ala Leu Gly Asn Ser Pro Tyr His Arg Ala
65 70 75 80

Pro Arg Cys Ile His Val Tyr Lys Lys Asn Gly Val Gly Lys Val Gly
85 90 95

Asp Gln Ile Leu Leu Ala Ile Lys Gly Gln Lys Lys Lys Ala Leu Ile
100 105 110

Val Gly His Cys Met Pro Gly Pro Arg Met Thr Pro Arg Phe Asp Ser
115 120 125

Asn Asn Val Val Leu Ile Glu Asp Asn Gly Asn Pro Val Gly Thr Arg
130 135 140

Ile Lys Thr Pro Ile Pro Thr Ser Leu Arg Lys Arg Glu Gly Glu Tyr
145 150 155 160

Ser Lys Val Leu Ala Ile Ala Gln Asn Phe Val
165 170

<210> 384
<211> 171
<212> PRT
<213> Homo sapiens

<400> 384
Ala Arg Val Val Gln Pro Ala Ala Arg Ala Gly Met Trp Ala Gly Gly
1 5 10 15

Arg Ser Ser Cys Gln Ala Glu Val Leu Arg Ala Thr Arg Gly Gly Ala
20 25 30

Ala Arg Gly Asn Ala Ala Pro Gly Arg Ala Leu Glu Met Val Pro Gly
35 40 45

Ala Ala Gly Trp Cys Cys Leu Val Leu Trp Leu Pro Ala Cys Val Ala
50 55 60

Ala His Gly Phe Arg Ile His Asp Tyr Leu Tyr Phe Gln Val Leu Ser
65 70 75 80

208

Pro Gly Asp Ile Arg Tyr Ile Phe Thr Ala Thr Pro Ala Lys Asp Phe
85 90 95

Gly Gly Ile Phe His Thr Arg Tyr Glu Gln Ile His Leu Val Pro Ala
100 105 110

Glu Pro Pro Glu Ala Cys Gly Glu Leu Ser Asn Gly Phe Phe Ile Gln
115 120 125

Asp Gln Ile Ala Leu Val Glu Arg Gly Gly Cys Ser Phe Leu Ser Lys
130 135 140

Thr Arg Val Val Gln Glu His Gly Gly Arg Ala Val Ile Ile Ser Asp
145 150 155 160

Asn Ala Leu Thr Met Thr Ala Ser Thr Trp Arg
165 170

<210> 385
<211> 187
<212> PRT
<213> Homo sapiens

<400> 385
Ile Ala Thr Ala Ala Leu Phe Phe Phe Phe Tyr Cys Gln Val Ala Gly
1 5 10 15

Phe Ile Gly Lys Gly Gln Ser Leu Arg Ser Trp Val Pro Gln Arg Leu
20 25 30

Leu Gly Leu Glu Pro Gln Leu Gln Pro Met Gln Gln Ser Arg Leu Leu
35 40 45

Leu Pro Phe Leu Phe Phe Leu Leu Glu Gly Cys Ala Pro Ser Ser Leu
50 55 60

Gly Pro Gly Ala Ala Pro Gly Ser Gly His Ser Leu Gly Pro Pro Gly
65 70 75 80

Ser Pro Gly Ala Pro Gly Pro Gln Pro Ala Val Gly Pro Ser Ser Pro
85 90 95

Cys Gln Pro Gly Pro Ser Pro Ser Ser Pro Ala Ala Ala Ala Ala Ser
100 105 110

Ser Gln Ser Ser Val Ala Ser Trp Pro Cys Thr Leu Arg Cys Ala Ala
115 120 125

Pro Ser Pro Asp Ala Ser Ala Leu Arg Pro Ala Ala Ser Pro Ala Ala
130 135 140

Thr Pro Ala Trp Ser Pro Gly Ser Gly Thr Ile Arg Val Leu Arg Pro
145 150 155 160

Pro Ala Pro Ala Ala Ala Pro Ala Thr Ala Ile Thr Asn Arg Gly Pro
165 170 175

Pro Arg Arg Arg Arg Arg Asn Ala Arg Thr Ala
180 185

<210> 386
<211> 194
<212> PRT
<213> Homo sapiens

<400> 386
Glu Arg Pro Pro Pro Arg Arg Thr Gly Thr Pro Val Ala Arg Pro Arg
1 5 10 15

Gly Pro Pro Asp Pro Ala Val Ala Ala Gly Thr Ala Leu Arg Ala Lys
20 25 30

Gln Phe Ala Arg Tyr Gly Ala Ala Ser Gly Val Val Pro Gly Ser Leu
35 40 45

Trp Pro Ser Pro Glu Gln Leu Arg Glu Leu Glu Ala Glu Glu Arg Glu
50 55 60

Trp Tyr Pro Ser Leu Ala Thr Met Gln Glu Ser Leu Arg Val Lys Gln
65 70 75 80

Leu Ala Glu Glu Gln Lys Arg Arg Glu Arg Glu Gln His Ile Ala Glu
85 90 95

Cys Met Ala Lys Met Pro Gln Met Ile Val Asn Trp Gln Gln Gln Gln
100 105 110

Arg Glu Asn Trp Glu Lys Ala Gln Ala Asp Lys Glu Arg Arg Ala Arg
115 120 125

Leu Gln Ala Glu Ala Gln Glu Leu Leu Gly Tyr Gln Val Asp Pro Arg
130 135 140

Ser Ala Arg Phe Gln Glu Leu Leu Gln Asp Leu Glu Lys Lys Glu Arg
145 150 155 160

Asn Pro Gln Gly Gly Lys Thr Glu Thr Glu Glu Gly Gly Ala Thr Ala
165 170 175

Ala Leu Ala Ala Ala Val Ala Gln Asp Pro Ala Ala Ser Gly Ala Pro
180 185 190

Ser Ser

<210> 387
<211> 113
<212> PRT
<213> Homo sapiens

<400> 387
Tyr Gln Ser Leu Ala Glu Thr Gln Gln Lys Lys Glu Asn Phe Arg Pro
1 5 10 15

Ile Ser Leu Lys Asn Thr Asp Ala Lys Ile Leu Asn Lys Ile Leu Ala
20 25 30

Asn Gln Ile Gln Gln His Ile Lys Lys Leu Ile His Asn Asp Arg Val

210

35 40 45

Gly Phe Ile Pro Glu Met Gln Gly Trp Phe Asn Ile Cys Lys Ser Ile
50 55 60

Asn Ile Val His His Ile Asn Arg Thr Lys Asp Lys Asn His Met Ile
65 70 75 80

Ile Ser Ile Asp Ala Glu Lys Ala Phe Asp Lys Ile Arg Gln Ser Phe
85 90 95

Met Leu Lys Thr Leu Asn Lys Leu Gly Ile His Gly Met Tyr Leu Gly
100 105 110

Arg

<210> 388
<211> 101
<212> PRT
<213> Homo sapiens

<400> 388
Lys Lys Glu Asn Phe Arg Pro Ile Ser Leu Lys Asn Thr Asp Ala Lys
1 5 10 15

Ile Leu Asn Lys Ile Leu Ala Asn Gln Ile Gln Gln His Ile Lys Lys
20 25 30

Leu Ile His Asn Asp Arg Val Gly Phe Ile Pro Glu Met Gln Gly Trp
35 40 45

Phe Asn Ile Cys Lys Ser Ile Asn Ile Val His His Ile Asn Arg Thr
50 55 60

Lys Asp Lys Asn His Met Ile Ile Ser Ile Asp Ala Glu Lys Ala Phe
65 70 75 80

Asp Lys Ile Arg Gln Ser Phe Met Leu Lys Thr Leu Asn Lys Leu Gly
85 90 95

Ile His Gly Met Tyr
100

<210> 389
<211> 11
<212> PRT
<213> Homo sapiens

<400> 389
Asp Ala Lys Ile Leu Asn Lys Ile Leu Ala Asn
1 5 10

<210> 390
<211> 10
<212> PRT
<213> Homo sapiens

<400> 390

211

Ile Gln Gln His Ile Lys Lys Leu Ile His
1 5 10

<210> 391
<211> 19
<212> PRT
<213> Homo sapiens

<400> 391
Lys Asp Lys Asn His Met Ile Ile Ser Ile Asp Ala Glu Lys Ala Phe
1 5 10 15

Asp Lys Ile

<210> 392
<211> 10
<212> PRT
<213> Homo sapiens

<400> 392
Met Leu Lys Thr Leu Asn Lys Leu Gly Ile
1 5 10

<210> 393
<211> 10
<212> PRT
<213> Homo sapiens

<400> 393
Lys Lys Glu Asn Phe Arg Pro Ile Ser Leu
1 5 10

<210> 394
<211> 85
<212> PRT
<213> Homo sapiens

<400> 394
Trp Thr Met Phe Ile Asp Leu His Met Leu Asn Gln Pro Cys Ile Ser
1 5 10 15

Gly Met Lys Pro Thr Arg Ser Leu Trp Ile Ser Phe Leu Met Cys Cys
20 25 30

Trp Ile Trp Phe Ala Asn Ile Leu Leu Arg Ile Phe Ala Ser Val Phe
35 40 45

Phe Arg Asp Ile Gly Leu Lys Phe Ser Phe Phe Cys Cys Val Ser Ala
50 55 60

Arg Leu Trp Tyr Gln Asp Asp Ala Gly Leu Ile Asn Glu Leu Gly Arg
65 70 75 80

Ile Pro Ser Phe Tyr
85

<210> 395
<211> 72

<212> PRT
<213> Homo sapiens

<400> 395
Glu Arg Pro Glu Glu Gly Thr Glu Pro Ser Pro Ser Pro Val Ala Glu
1 5 10 15

Gln Ala Ser Val Ser Met Thr Pro Val Phe Arg Ala Trp Gly Leu Trp
20 25 30

Val Tyr Val Leu Pro Thr Gly Phe Pro Gly Pro Cys Cys Met Met Leu
35 40 45

Leu Glu Leu Phe Pro Lys Glu Ser Val Pro Gln Ala Tyr Gln Gly Ile
50 55 60

Leu Leu Tyr Leu His Phe Gly Phe
65 70

<210> 396
<211> 123
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (23)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (27)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (32)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (106)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 396
Arg Gly Glu Val Pro His Gln Pro His Pro Thr Arg Arg Thr Val Val
1 5 10 15

Ser Gly Gln Ala Pro Trp Xaa Pro Gly Pro Xaa Ala Leu Gly Gln Xaa
20 25 30

Val Glu Thr Ala Ala Gly Met Gly Met Pro Leu Val Thr Val Thr Ala
35 40 45

Ala Thr Phe Pro Thr Leu Ser Cys Pro Pro Arg Ala Trp Pro Glu Val
50 55 60

Glu Ala Pro Glu Ala Pro Ala Leu Pro Val Val Pro Glu Leu Pro Glu
65 70 75 80

Val Pro Met Glu Met Pro Leu Val Leu Pro Pro Glu Leu Glu Leu Leu
85 90 95

Ser Leu Glu Ala Val His Arg Tyr Gln Xaa Gly Gly Thr Leu Met Gly
100 105 110

Trp Thr Arg Ala Glu Ala Ser Ala Asn Gly Ser
115 120

<210> 397
<211> 133
<212> PRT
<213> Homo sapiens

<400> 397
Met Val Leu Asp Pro Tyr Arg Ala Val Ala Leu Glu Leu Gln Ala Asn
1 5 10 15

Arg Glu Pro Asp Phe Ser Ser Leu Val Ser Pro Leu Ser Pro Arg Arg
20 25 30

Met Ala Ala Arg Val Phe Tyr Leu Leu Leu Gly Glu Cys Met His Val
35 40 45

Cys Val Cys Met Trp Gly Arg Asp Thr Glu Thr Arg Gly Pro Tyr Arg
50 55 60

Asp Ser Pro Asp Leu Pro Ser Pro Arg Leu Leu Thr Ser Ala Leu Ser
65 70 75 80

Ala Thr Asp Ser Ser Arg Glu Thr Arg Lys Ala Ile Trp Ser Pro Pro
85 90 95

Asp Pro Ala Gly Ala Gln Ile Pro Leu Arg Leu Glu Ser Ile Tyr Lys
100 105 110

Ala Ala Arg Lys Pro Ala Thr Ser Ser Lys Pro Arg Arg Ala Ser Leu
115 120 125

Lys Lys Lys Lys Lys
130

<210> 398
<211> 11
<212> PRT
<213> Homo sapiens

<400> 398
Ala Phe Arg Asn Leu Pro Asn Leu Arg Ile Leu
1 5 10

<210> 399
<211> 13
<212> PRT
<213> Homo sapiens

<400> 399
Ala Phe Gln Gly Leu Phe His Leu Phe Glu Leu Arg Leu

1 5 10

<210> 400
<211> 206
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (3)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 400
Asn Lys Xaa Ile Leu Glu Val Pro Ser Ala Arg Thr Thr Arg Ile Met
1 5 10 15

Gly Asp His Leu Asp Leu Leu Leu Gly Val Val Leu Met Ala Gly Pro
20 25 30

Val Phe Gly Ile Pro Ser Cys Ser Phe Asp Gly Arg Ile Ala Phe Tyr
35 40 45

Arg Phe Cys Asn Leu Thr Gln Val Pro Gln Val Leu Asn Thr Thr Glu
50 55 60

Arg Leu Leu Leu Ser Phe Asn Tyr Ile Arg Thr Val Thr Ala Ser Ser
65 70 75 80

Phe Pro Phe Leu Glu Gln Leu Gln Leu Leu Glu Leu Gly Ser Gln Tyr
85 90 95

Thr Pro Leu Thr Ile Asp Lys Glu Ala Phe Arg Asn Leu Pro Asn Leu
100 105 110

Arg Ile Leu Asp Leu Gly Ser Ser Lys Ile Tyr Phe Leu His Pro Asp
115 120 125

Ala Phe Gln Gly Leu Phe His Leu Phe Glu Leu Arg Leu Tyr Phe Cys
130 135 140

Gly Leu Ser Asp Ala Val Leu Lys Asp Gly Tyr Phe Arg Asn Leu Lys
145 150 155 160

Ala Leu Thr Arg Leu Asp Leu Ser Lys Asn Gln Ile Arg Ser Leu Tyr
165 170 175

Leu His Pro Ser Phe Gly Lys Leu Asn Ser Leu Lys Ser Ile Asp Phe
180 185 190

Ser Ser Asn Gln Ile Phe Leu Val Cys Glu His Glu Leu Glu
195 200 205

<210> 401
<211> 261
<212> PRT
<213> Homo sapiens

<400> 401
Ala His Ala Ala Leu Gln Leu Ser Leu Arg Thr Cys Gly Pro Cys Ser

215

1 5 10 15

Ser Pro Tyr Pro His Ala Gly Leu Ala Ala Leu Leu Thr His Met Trp
20 25 30

Ala Leu Gln Leu Ser Leu Pro Thr Cys Gly Leu Ala Ala Leu Leu Thr
35 40 45

His Met Arg Pro Cys Ser Ser Pro Tyr Pro His Ala Gly Leu Ala Ala
50 55 60

Leu Leu Thr His Met Gly Pro Cys Arg Ser Pro Tyr Pro His Gly Gly
65 70 75 80

Leu Ala Ala Val Leu Thr His Met Arg Ala Leu Gln Leu Ser Leu Pro
85 90 95

Thr Trp Gly Leu Ala Ala Leu Leu Thr His Met Arg Pro Cys Ser Ser
100 105 110

Pro Tyr Pro His Ala Gly Leu Ala Cys Cys Trp Leu Trp Ser Leu Ser
115 120 125

Ser His Arg Ser Leu Gln Val Gln Ala Thr His Arg Leu Val Val Arg
130 135 140

Thr Ile Lys Asp Arg Val Met Leu Lys Val Leu Pro Gln Thr Arg Arg
145 150 155 160

Arg Gly Pro Phe Leu Ser Ser Cys Arg Asn Asp Val Met Arg Asn Cys
165 170 175

Val Pro Arg His Ala Val Leu Val Thr Thr Cys Val Phe Val Ser Phe
180 185 190

Pro Thr His Cys Lys Val Gly Ile Thr Gly Pro Ile Thr Gln Val Lys
195 200 205

Gln Lys Pro Gly Asn His Ser Ser Pro Cys Pro Val Ile Gln Leu Val
210 215 220

Ala Lys Ala Glu Phe Glu Leu Met Leu Pro Ser Val Pro Lys Pro Val
225 230 235 240

Tyr Leu Thr Leu Val Leu Ser Cys Trp Cys Leu Cys Asp Val Pro Cys
245 250 255

Leu Ser Val Ser Leu
260

<210> 402
<211> 17
<212> PRT
<213> Homo sapiens

<400> 402
Leu Ala Cys Cys Trp Leu Trp Ser Leu Ser Ser His Arg Ser Leu Gln
1 5 10 15

Val

<210> 403
<211> 67
<212> PRT
<213> Homo sapiens

<400> 403
Met Gly Glu Ala Ser Pro Pro Ala Pro Ala Arg Arg His Leu Leu Val
1 5 10 15

Leu Leu Leu Leu Leu Ser Thr Leu Val Ile Pro Ser Ala Ala Ala Pro
20 25 30

Ile His Asp Ala Asp Ala Gln Glu Ser Ser Leu Gly Leu Thr Gly Leu
35 40 45

Gln Ser Leu Leu Gln Gly Phe Ser Arg Leu Phe Leu Lys Val Thr Cys
50 55 60

Phe Gly Ala
65

<210> 404
<211> 90
<212> PRT
<213> Homo sapiens

<400> 404
Met Leu Val Val Ser Thr Val Ile Ile Val Phe Trp Glu Phe Ile Asn
1 5 10 15

Ser Thr Glu Gly Ser Phe Leu Trp Ile Tyr His Ser Lys Asn Pro Glu
20 25 30

Val Asp Asp Ser Ser Ala Gln Lys Gly Trp Trp Phe Leu Ser Trp Phe
35 40 45

Asn Asn Gly Ile His Asn Tyr Gln Gln Gly Glu Glu Asp Ile Asp Lys
50 55 60

Glu Lys Gly Arg Glu Glu Thr Lys Gly Arg Lys Met Thr Gln Gln Ser
65 70 75 80

Phe Gly Tyr Gly Thr Gly Leu Ile Gln Thr
85 90

<210> 405
<211> 18
<212> PRT
<213> Homo sapiens

<400> 405
Phe Pro Gly Arg Thr His Ala Ser Gly Asn Val Lys Gly Lys Val Ile
1 5 10 15

Leu Ser

<210> 406
<211> 106
<212> PRT
<213> Homo sapiens

<400> 406
Ala Asp Gln Glu Lys Ile Arg Asn Val Lys Gly Lys Val Ile Leu Ser
1 5 10 15

Met Leu Val Val Ser Thr Val Ile Ile Val Phe Trp Glu Phe Ile Asn
20 25 30

Ser Thr Glu Gly Ser Phe Leu Trp Ile Tyr His Ser Lys Asn Pro Glu
35 40 45

Val Asp Asp Ser Ser Ala Gln Lys Gly Trp Trp Phe Leu Ser Trp Phe
50 55 60

Asn Asn Gly Ile His Asn Tyr Gln Gln Gly Glu Glu Asp Ile Asp Lys
65 70 75 80

Glu Lys Gly Arg Glu Glu Thr Lys Gly Arg Lys Met Thr Gln Gln Ser
85 90 95

Phe Gly Tyr Gly Thr Gly Leu Ile Gln Thr
100 105

<210> 407
<211> 236
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (50)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 407
Met Gln Ser Pro Leu Val Glu Cys Pro Pro Pro Ser Ile His Tyr Trp
1 5 10 15

Pro Ser Val Pro Ala Gly Ala Gln Gly Ala Cys Ser Pro Met Phe His
20 25 30

Ala Ala Gly Trp Ser Arg Ser Gln Pro Asn Gly Glu Ile Pro Ala Ser
35 40 45

Ser Xaa Gly His Leu Ser Ile Gln Arg Ala Ala Leu Val Val Leu Glu
50 55 60

Asn Tyr Tyr Lys Asp Phe Thr Ile Tyr Asn Pro Asn Leu Leu Thr Ala
65 70 75 80

Ser Lys Phe Arg Ala Ala Lys His Met Ala Gly Leu Lys Val Tyr Asn
85 90 95

Val Asp Gly Pro Ser Asn Asn Ala Thr Gly Gln Ser Arg Ala Met Ile
100 105 110

```
Ala Ala Ala Ala Arg Arg Arg Asp Ser Ser His Asn Glu Leu Tyr Tyr
        115                 120                 125

Glu Glu Ala Glu His Glu Arg Arg Val Lys Lys Arg Lys Ala Arg Leu
    130                 135                 140

Val Val Ala Val Glu Glu Ala Phe Ile His Ile Gln Arg Leu Gln Ala
145                 150                 155                 160

Glu Glu Gln Gln Lys Ala Pro Gly Glu Val Met Asp Pro Arg Glu Ala
                165                 170                 175

Ala Gln Ala Ile Phe Pro Ser Met Ala Arg Ala Leu Gln Lys Tyr Leu
            180                 185                 190

Arg Ile Thr Arg Gln Gln Asn Tyr His Ser Met Glu Ser Ile Leu Gln
        195                 200                 205

Ala Pro Gly Leu Leu His His Gln Arg His Asp Pro Gln Gly Leu Pro
    210                 215                 220

Arg Thr Val Pro Gln Cys Gly Pro His Pro Ala Ile
225                 230                 235
```

<210> 408
<211> 23
<212> PRT
<213> Homo sapiens

<400> 408

```
Leu Ser Ile Gln Arg Ala Ala Leu Val Val Leu Glu Asn Tyr Tyr Lys
  1               5                  10                  15

Asp Phe Thr Ile Tyr Asn Pro
             20
```

<210> 409
<211> 15
<212> PRT
<213> Homo sapiens

<400> 409

```
Asp Ser Ser His Asn Glu Leu Tyr Tyr Glu Glu Ala Glu His Glu
  1               5                  10                  15
```

<210> 410
<211> 18
<212> PRT
<213> Homo sapiens

<400> 410

```
Phe Pro Ser Met Ala Arg Ala Leu Gln Lys Tyr Leu Arg Ile Thr Arg
  1               5                  10                  15

Gln Gln
```

<210> 411

<211> 140
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (117)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 411
Met Ala Phe Lys Leu Leu Ile Leu Leu Ile Gly Thr Trp Ala Leu Phe
1 5 10 15

Phe Arg Lys Arg Arg Ala Asp Met Pro Arg Val Phe Val Phe Arg Ala
20 25 30

Leu Leu Leu Val Leu Ile Phe Leu Phe Cys Gly Phe Pro Ile Gly Phe
35 40 45

Phe Thr Gly Ser Ala Phe Trp Thr Leu Gly Asn Arg Asn Tyr Gln Gly
50 55 60

Ile Val Gln Tyr Ala Val Ser Pro Cys Gly Met Pro Ser Ser Phe His
65 70 75 80

Pro Leu Leu Ala Ile Arg Pro Cys Trp Ser Ser Gly Ser Leu Gln Pro
85 90 95

Asn Val Pro Arg Cys Arg Leu Val Pro Leu Pro Thr Glu Trp Gly Asn
100 105 110

Pro Arg Phe Gln Xaa Gly Thr Pro Glu Tyr Pro Ala Ser Ser Ile Gly
115 120 125

Gly Pro Arg Lys Leu Leu Gln Arg Phe His His Leu
130 135 140

<210> 412
<211> 37
<212> PRT
<213> Homo sapiens

<400> 412
Met Gly Leu Pro Val Ser Trp Ala Pro Pro Ala Leu Trp Val Leu Gly
1 5 10 15

Cys Cys Ala Leu Leu Leu Ser Leu Trp Ala Leu Cys Thr Ala Cys Arg
20 25 30

Ser Pro Arg Thr Leu
35

<210> 413
<211> 20
<212> PRT
<213> Homo sapiens

<400> 413
Ile Tyr Gly Lys Thr Gly Gln Pro Asp Lys Ile Tyr Val Glu Leu His

220
1 5 10 15

Gln Asn Ser Pro
20

<210> 414
<211> 16
<212> PRT
<213> Homo sapiens

<400> 414
Phe Leu Glu Pro Leu Ser Gly Leu Tyr Thr Cys Thr Leu Ser Tyr Lys
1 5 10 15

<210> 415
<211> 16
<212> PRT
<213> Homo sapiens

<400> 415
Leu Gln Val Val Arg Leu Asp Ser Cys Arg Pro Gly Phe Gly Lys Asn
1 5 10 15

<210> 416
<211> 12
<212> PRT
<213> Homo sapiens

<400> 416
Cys Val Ser Val Leu Thr Tyr Gly Ala Lys Ser Cys
1 5 10

<210> 417
<211> 308
<212> PRT
<213> Homo sapiens

<400> 417
Pro Ala Lys Gly Glu Gly Cys Arg Arg Leu His Asp His Pro His Ile
1 5 10 15

Trp Arg Leu Leu Trp Ala His Ser Asp Pro Asp Pro Leu Pro Thr Gln
20 25 30

Pro Arg Ala Glu Gln Gly Glu Thr Glu Phe Cys Val Pro Val Gly Pro
35 40 45

Leu Cys His Asp Trp His Pro Leu Pro Val Asp Val Leu Ala Gln Leu
50 55 60

Gln Leu Ser His Ile Leu Pro Trp Gly Gln Pro Ala Pro Ser Arg His
65 70 75 80

Gln His Leu Leu Leu Leu Gly Ser Leu Arg Ala Tyr Leu Gly Gly Asn
85 90 95

Ile Gln Cys Pro Ala Lys Lys Gly Lys Leu Asp Met Val His Ile Gln
100 105 110

Asn Ala Thr Leu Ala Gly Gly Val Ala Val Gly Thr Ala Ala Glu Met
115 120 125

Met Leu Met Pro Tyr Gly Ala Leu Ile Ile Gly Phe Val Cys Gly Ile
130 135 140

Ile Ser Thr Leu Gly Phe Val Tyr Leu Thr Pro Phe Leu Glu Ser Arg
145 150 155 160

Leu His Ile Gln Asp Thr Cys Gly Ile Asn Asn Leu His Gly Ile Pro
165 170 175

Gly Ile Ile Gly Gly Ile Val Gly Ala Val Thr Ala Ala Ser Ala Ser
180 185 190

Leu Glu Val Tyr Gly Lys Glu Gly Leu Val His Ser Phe Asp Phe Gln
195 200 205

Gly Phe Asn Gly Asp Trp Thr Ala Arg Thr Gln Gly Lys Phe Gln Ile
210 215 220

Tyr Gly Leu Leu Val Thr Leu Ala Met Ala Leu Met Gly Gly Ile Ile
225 230 235 240

Val Gly Leu Ile Leu Arg Leu Pro Phe Trp Gly Gln Pro Ser Asp Glu
245 250 255

Asn Cys Phe Glu Asp Ala Val Tyr Trp Glu Met Pro Glu Gly Asn Ser
260 265 270

Thr Val Tyr Ile Pro Glu Asp Pro Thr Phe Lys Pro Ser Gly Pro Ser
275 280 285

Val Pro Ser Val Pro Met Val Ser Pro Leu Pro Met Ala Ser Ser Val
290 295 300

Pro Leu Val Pro
305

<210> 418
<211> 108
<212> PRT
<213> Homo sapiens

<400> 418
Pro Arg Val Arg Thr Arg Ala Pro Val Val Pro Pro Ala Gly His Arg
1 5 10 15

Ala Leu Ser Pro Ala Gly Val Leu Leu Ala Val Pro Ala Met Leu Ser
20 25 30

Leu Asp Phe Leu Asp Asp Val Arg Arg Met Asn Lys Arg Gln Val Ser
35 40 45

Leu Ser Val Leu Phe Phe Ser Trp Leu Phe Leu Ser Leu Arg Gly Cys
50 55 60

Cys Cys Gly Ala Arg Arg Thr Pro Gly Phe Trp Cys Glu Gly Leu Ser
65 70 75 80

Trp Ser Asp Thr Arg Val Ile Arg Phe Leu Trp Arg Leu Trp Pro Glu
85 90 95

Ala Ala Leu Ser Ala Ser Leu Phe Leu Thr Pro Asn
100 105

<210> 419
<211> 16
<212> PRT
<213> Homo sapiens

<400> 419
His Ala Ser Ala Trp Asn Leu Ile Leu Leu Thr Val Phe Thr Leu Ser
1 5 10 15

<210> 420
<211> 24
<212> PRT
<213> Homo sapiens

<400> 420
Val Tyr Ala Ala Leu Gly Ala Gly Val Phe Thr Leu Phe Leu Ala Leu
1 5 10 15

Asp Thr Gln Leu Leu Met Gly Asn
20

<210> 421
<211> 18
<212> PRT
<213> Homo sapiens

<400> 421
Glu Glu Tyr Ile Phe Gly Ala Leu Asn Ile Tyr Leu Asp Ile Ile Tyr
1 5 10 15

Ile Phe

<210> 422
<211> 26
<212> PRT
<213> Homo sapiens

<400> 422
Trp Asn Leu Ile Leu Leu Thr Val Phe Thr Leu Ser Met Ala Tyr Leu
1 5 10 15

Thr Gly Met Leu Ser Ser Tyr Tyr Asn Thr

223

20 25

<210> 423
<211> 11
<212> PRT
<213> Homo sapiens

<400> 423
Thr Leu Ser Leu Leu Val Ser Leu His Thr Val
1 5 10

<210> 424
<211> 241
<212> PRT
<213> Homo sapiens

<400> 424
Met Ser Ser Ser Gly Thr Ser Asp Ala Ser Pro Ser Gly Ser Pro Val
1 5 10 15

Leu Ala Ser Tyr Lys Pro Ala Pro Pro Lys Asp Lys Leu Pro Glu Thr
20 25 30

Pro Arg Arg Arg Met Lys Lys Ser Leu Ser Ala Pro Leu His Pro Glu
35 40 45

Phe Glu Glu Val Tyr Arg Phe Gly Ala Glu Ser Arg Lys Leu Leu Leu
50 55 60

Arg Glu Pro Val Asp Ala Met Pro Asp Pro Thr Pro Phe Leu Leu Ala
65 70 75 80

Arg Glu Ser Ala Glu Val His Leu Ile Lys Glu Arg Pro Leu Val Ile
85 90 95

Pro Pro Ile Ala Ser Asp Arg Ser Gly Glu Gln His Ser Pro Ala Arg
100 105 110

Glu Lys Pro His Lys Ala His Val Gly Val Ala His Arg Ile His His
115 120 125

Ala Thr Pro Pro Gln Pro Ala Arg Gly Glu Asp Pro Gly Gly Arg Pro
130 135 140

Gly Glu Arg Arg Gln Gly Gly Glu Glu Ala Leu Arg Asp Gly Gln Asn
145 150 155 160

Cys Val Lys Pro Ala Val Pro His Pro Ala Leu Ser Met His Cys Glu
165 170 175

His His Trp Glu Ile Ser Ala Thr Pro Phe Leu Phe Asn Pro Met His
180 185 190

Ala Lys His Phe Ser His Leu Pro Thr His Ser Pro Ser Ala Ser Leu
195 200 205

Ala Leu Phe Phe Thr Pro Lys Tyr Asp Arg Val Pro Ala Ala Glu Tyr
210 215 220

224

Val Phe Pro Asn Cys Cys Gly Gln Thr Pro Val Cys Arg Ile Ala Cys
225 230 235 240

Phe

<210> 425
<211> 85
<212> PRT
<213> Homo sapiens

<400> 425
Met Ser Ser Ser Gly Thr Ser Asp Ala Ser Pro Ser Gly Ser Pro Val
1 5 10 15

Leu Ala Ser Tyr Lys Pro Ala Pro Pro Lys Asp Lys Leu Pro Glu Thr
20 25 30

Pro Arg Arg Arg Met Lys Lys Ser Leu Ser Ala Pro Leu His Pro Glu
35 40 45

Phe Glu Glu Val Tyr Arg Phe Gly Ala Glu Ser Arg Lys Leu Leu Leu
50 55 60

Arg Glu Pro Val Asp Ala Met Pro Asp Pro Thr Pro Phe Leu Leu Ala
65 70 75 80

Arg Glu Ser Ala Glu
85

<210> 426
<211> 63
<212> PRT
<213> Homo sapiens

<400> 426
Val His Leu Ile Lys Glu Arg Pro Leu Val Ile Pro Pro Ile Ala Ser
1 5 10 15

Asp Arg Ser Gly Glu Gln His Ser Pro Ala Arg Glu Lys Pro His Lys
20 25 30

Ala His Val Gly Val Ala His Arg Ile His His Ala Thr Pro Pro Gln
35 40 45

Pro Ala Arg Gly Glu Asp Pro Gly Gly Arg Pro Gly Glu Arg Arg
50 55 60

<210> 427
<211> 93
<212> PRT
<213> Homo sapiens

<400> 427
Gln Gly Gly Glu Glu Ala Leu Arg Asp Gly Gln Asn Cys Val Lys Pro
1 5 10 15

Ala Val Pro His Pro Ala Leu Ser Met His Cys Glu His His Trp Glu
20 25 30

Ile Ser Ala Thr Pro Phe Leu Phe Asn Pro Met His Ala Lys His Phe
35 40 45

Ser His Leu Pro Thr His Ser Pro Ser Ala Ser Leu Ala Leu Phe Phe
50 55 60

Thr Pro Lys Tyr Asp Arg Val Pro Ala Ala Glu Tyr Val Phe Pro Asn
65 70 75 80

Cys Cys Gly Gln Thr Pro Val Cys Arg Ile Ala Cys Phe
85 90

<210> 428
<211> 59
<212> PRT
<213> Homo sapiens

<400> 428
Lys Arg Ala Ser Gln Pro Pro Cys Thr Arg Asn Leu Lys Arg Ser Thr
1 5 10 15

Asp Ser Gly Gln Arg Ala Gly Asn Ser Phe Cys Gly Asn Gln Trp Met
20 25 30

Leu Cys Pro Thr Pro Pro His Phe Cys Trp Leu Gly Ser Pro Pro Arg
35 40 45

Ser Thr Ser Ser Lys Arg Gly Pro Ser Ser Ser
50 55

<210> 429
<211> 65
<212> PRT
<213> Homo sapiens

<400> 429
Pro Pro Ser Pro Pro Thr Glu Ala Ala Ser Ser Thr Ala Arg Pro Ala
1 5 10 15

Lys Ser Arg Thr Arg Pro Thr Ser Gly Trp His Ile Gly Ser Thr Thr
20 25 30

Pro Pro Arg Arg Ser Gln Pro Glu Val Lys Thr Leu Ala Val Asp Gln
35 40 45

Val Asn Gly Gly Lys Val Val Arg Lys His Ser Gly Thr Asp Arg Thr
50 55 60

Val
65

<210> 430
<211> 148
<212> PRT
<213> Homo sapiens

<400> 430
Met Trp Asn Pro Asn Ala Gly Gln Pro Gly Pro Asn Pro Tyr Pro Pro

```
  1               5                  10                  15

Asn Ile Gly Cys Pro Gly Gly Ser Asn Pro Ala His Pro Pro Pro Ile
             20                  25                  30

Asn Pro Pro Phe Pro Pro Gly Pro Cys Pro Pro Pro Pro Gly Ala Pro
         35                  40                  45

His Gly Asn Pro Ala Phe Pro Pro Gly Gly Pro Pro His Pro Val Pro
     50                  55                  60

Gln Pro Gly Tyr Pro Gly Cys Gln Pro Leu Gly Pro Tyr Pro Pro Pro
 65                  70                  75                  80

Tyr Pro Pro Pro Ala Pro Gly Ile Pro Pro Val Asn Pro Leu Ala Pro
                 85                  90                  95

Gly Met Val Gly Pro Ala Val Ile Val Asp Lys Lys Met Gln Lys Lys
            100                 105                 110

Met Lys Lys Ala His Lys Lys Met His Lys His Gln Lys His His Lys
        115                 120                 125

Tyr His Lys His Gly Lys His Ser Ser Ser Ser Ser Ser Ser Ser Ser
    130                 135                 140

Ser Asp Ser Asp
145
```

<210> 431
<211> 58
<212> PRT
<213> Homo sapiens

<400> 431

```
Arg Val Gly Pro Asp Ala Trp Ala Asp Ala Trp Glu Gln Ala Gln Ala
  1               5                  10                  15

Ala Val Glu Arg Leu Glu Asp Thr Pro Lys His Val Glu Ser Gln Cys
             20                  25                  30

Arg Ala Ala Arg Ala Lys Ser Ile Ser Pro Gln Tyr Trp Val Pro Trp
         35                  40                  45

Arg Phe Gln Ser Cys Pro Pro Thr Thr Tyr
     50                  55
```

<210> 432
<211> 84
<212> PRT
<213> Homo sapiens

<400> 432

```
Ser Thr Leu Ser Pro Arg Pro Leu Ser Ser Ser Pro Arg Ser Ser Pro
  1               5                  10                  15

Trp Gln Ser Ser Phe Pro Pro Arg Trp Ala Pro Ser Ser Cys Ala Thr
             20                  25                  30
```

Ala Arg Val Ser Arg Met Pro Thr Val Gly Ser Leu Pro Ser Ser Ile
35 40 45

Pro Thr Ala Cys Pro Trp Asn Pro Ser Cys Glu Ser Leu Gly Ser Trp
50 55 60

His Gly Trp Thr Ser Ser Asp Ser Arg Gln Glu Asp Ala Glu Glu Asn
65 70 75 80

Glu Glu Ser Ser

<210> 433
<211> 86
<212> PRT
<213> Homo sapiens

<400> 433
Met Pro Gly Ser Gln Gly Gln Ile His Ile Pro Pro Ile Leu Gly Ala
1 5 10 15

Leu Glu Val Pro Ile Leu Pro Thr His His Leu Leu Ile His Pro Phe
20 25 30

Pro Gln Ala Pro Val Leu Leu Pro Gln Glu Leu Pro Met Ala Ile Gln
35 40 45

Leu Ser Pro Gln Val Gly Pro Leu Ile Leu Cys His Ser Gln Gly Ile
50 55 60

Gln Asp Ala Asn Arg Trp Val Pro Thr Leu Leu His Thr His Arg Leu
65 70 75 80

Pro Leu Glu Ser Leu Leu
85

<210> 434
<211> 65
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (56)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 434
Met Ala Ser Ile Pro Pro Leu Pro Pro Pro Leu Pro Ala Val Ile Leu
1 5 10 15

Thr Glu Tyr Arg Pro Trp Thr Leu Pro Ser Ser Leu Thr Ser Ser Ala
20 25 30

Leu Pro Ser Ser Phe Arg Cys His Val Val Leu Gly Glu Cys Ser Pro
35 40 45

Cys Ala Pro His Pro Leu Pro Xaa Pro Glu Pro His Pro Ala Val Glu
50 55 60

Pro
65

<210> 435
<211> 147
<212> PRT
<213> Homo sapiens

<400> 435
Pro Arg His Thr Tyr Trp Gly Ile Trp Leu Val Pro Ala Ala Met Ala
1 5 10 15

Ser Pro His Ser His Pro Ala Gln Gly Val Leu Gln Pro Pro Gly Pro
20 25 30

Gln Pro Arg Trp Glu Asp Arg Val Ala Leu Gly Thr Arg Gly Arg Ser
35 40 45

Pro Gly Ala Tyr Leu Thr Glu Ser Ala Pro Gln Gln Ala Ser Thr Thr
50 55 60

Pro Gly Pro Pro Thr Cys His Gly Lys Val Gly Ser Glu Trp Ala Trp
65 70 75 80

Leu Gly Ala Ala Pro Gly Pro Leu Pro Thr His Pro Ser His Tyr Ala
85 90 95

Ile Arg Val Pro Ser Asn Ile Cys Ser Cys Pro Gly Ala Ser Ser Ala
100 105 110

Pro Ala Leu Arg Gly Val Val Arg Gln Pro Pro Gly Pro Gln Asn Pro
115 120 125

Arg Gln Gly Gly Arg Arg Gly Thr Arg Ala Ser Pro Val Gly Ser Leu
130 135 140

Phe Cys Val
145

<210> 436
<211> 105
<212> PRT
<213> Homo sapiens

<400> 436
Met Phe Ala Val Leu Pro Ala Val Glu Gly Arg Ala Thr Pro His Gln
1 5 10 15

Asp Arg Thr Cys Tyr Pro Ser Arg Ser Arg Pro Trp Pro Ser Gln Pro
20 25 30

Ser Pro Arg Gly Ser Met Pro Val Pro Arg Pro Gly Ala Ala Arg Gly
35 40 45

Gln Leu Asp Gly His Val Gln Gly Gln Gly Trp Ala Leu Gln Trp Gly
50 55 60

Gly Pro Pro Ala Pro Ala Val Tyr Arg Arg Met Ala Leu Pro Pro Arg
65 70 75 80

```
Ala Ala Gly Ser Tyr Leu Asp Arg Lys Cys Pro His Pro Leu Pro Gly
                85                  90                  95

Ala Arg Leu Cys Pro Gly Leu Pro Leu
            100                 105

<210> 437
<211> 127
<212> PRT
<213> Homo sapiens

<400> 437
Val Phe Gly Ala Val Phe Leu Thr Thr Pro Ser His Asp Leu Ala Thr
  1               5                  10                  15

Pro Thr Gly Ala Ser Gly Trp Cys Leu Leu Pro Trp Pro Ala Pro Thr
             20                  25                  30

Leu Thr Leu His Arg Gly Ser Cys Ser Pro Gln Ala His Ser Leu Val
         35                  40                  45

Gly Arg Thr Gly Trp Pro Trp Gly Gln Glu Gly Gly Ala Gln Gly Leu
     50                  55                  60

Thr Ser Leu Arg Val Leu Pro Ser Arg His Pro Leu Pro Gln Gly Pro
 65                  70                  75                  80

Pro His Val Met Ala Arg Leu Val Val Asn Gly Pro Gly Trp Glu Gln
                85                  90                  95

Pro Leu Ala His Cys Pro Pro Thr His Leu Thr Met Gln Phe Glu Phe
            100                 105                 110

Gln Ala Thr Phe Ala Pro Ala Leu Gly Pro Ala Leu Pro Gln Pro
        115                 120                 125

<210> 438
<211> 186
<212> PRT
<213> Homo sapiens

<400> 438
His Glu Glu Pro Pro Ala Gly Phe Gly Leu Arg Ser Leu Trp Arg Arg
  1               5                  10                  15

Ser Pro Pro His Glu Val Gly Ala Arg Leu Pro Asn Gly Ala Phe Gly
             20                  25                  30

Phe Ser Val Arg Cys Leu Leu Cys Phe Pro Pro Trp Arg Ala Glu Pro
         35                  40                  45

Pro His Ile Arg Ile Gly Arg Ala Thr Pro Pro Gly Pro Gly Pro Gly
     50                  55                  60

Pro Ala Ser Pro Ala Leu Glu Ala Arg Cys Leu Cys Gln Gly Gln Gly
 65                  70                  75                  80

Gln Pro Glu Gly Ser Trp Met Ala Thr Cys Arg Val Lys Ala Gly Pro
```

230
85 90 95

Cys Ser Gly Ala Gly Arg Gln Pro Gln Gln Phe Thr Asp Ala Trp Leu
100 105 110

Phe Leu Pro Glu Gln Pro Ala Ala Thr Trp Thr Gly Asn Val Leu Ile
115 120 125

Pro Ser Leu Gly Pro Gly Ser Ala Leu Ala Phe Leu Cys Glu Pro Leu
130 135 140

Leu Ser Leu Cys Cys Leu Gly Thr Pro Asp Arg Gly Val Arg Val Cys
145 150 155 160

Pro Ser Val Thr Phe Tyr Ser Pro Arg Val Glu Glu Arg Lys Arg Gly
165 170 175

Lys Ser Lys Gly Val Gln Thr Pro Pro Gln
180 185

<210> 439
<211> 100
<212> PRT
<213> Homo sapiens

<400> 439
Met Ala Thr Cys Arg Val Lys Ala Gly Pro Cys Ser Gly Ala Gly Arg
1 5 10 15

Gln Pro Gln Gln Phe Thr Asp Ala Trp Leu Phe Leu Pro Glu Gln Pro
20 25 30

Ala Ala Thr Trp Thr Gly Asn Val Leu Ile Pro Ser Leu Gly Pro Gly
35 40 45

Ser Ala Leu Ala Phe Leu Cys Glu Pro Leu Leu Ser Leu Cys Cys Leu
50 55 60

Gly Thr Pro Asp Arg Gly Val Arg Val Cys Pro Ser Val Thr Phe Tyr
65 70 75 80

Ser Pro Arg Val Glu Glu Arg Lys Arg Gly Lys Ser Lys Gly Val Gln
85 90 95

Thr Pro Pro Gln
100

<210> 440
<211> 244
<212> PRT
<213> Homo sapiens

<400> 440
Met Lys Trp Phe Ser Thr Gln Pro Leu Trp Leu Asn Thr Lys Gln Arg
1 5 10 15

Ser His Arg Arg Gly Pro Gly Pro Pro Pro Ala Pro Leu Ser Gly Val
20 25 30

231

Leu Gly Ser Arg Gly Leu Pro His His Pro Ser Gln Gly Trp Gly Arg
35 40 45

Ala Gly Pro Arg Ala Gly Ala Asn Val Ala Trp Asn Ser Asn Cys Ile
50 55 60

Val Arg Trp Val Gly Gly Gln Trp Ala Arg Gly Cys Ser Gln Pro Gly
65 70 75 80

Pro Phe Thr Thr Asn Leu Ala Met Thr Cys Gly Gly Pro Trp Gly Ser
85 90 95

Gly Cys Leu Leu Gly Ser Thr Leu Ser Glu Val Ser Pro Trp Ala Pro
100 105 110

Pro Ser Cys Pro Gln Gly His Pro Val Leu Pro Thr Arg Leu Trp Ala
115 120 125

Trp Gly Leu Gln Asp Pro Leu Cys Arg Val Arg Val Gly Ala Gly His
130 135 140

Gly Ser Arg His Gln Pro Asp Ala Pro Val Gly Val Ala Arg Ser Trp
145 150 155 160

Asp Gly Val Val Arg Asn Thr Ala Pro Lys Thr Gln Asn Lys Asn Thr
165 170 175

Thr Asn Gly Arg Arg Ser Pro Pro Pro Thr Glu Val Gly Phe Glu Pro
180 185 190

Leu Leu Ile Phe Pro Val Ser Phe Leu Gln Pro Leu Val Ser Arg Lys
195 200 205

Ser Gln Thr Gly Thr His Ala His His Gly Gln Glu Ser Arg Asp Ser
210 215 220

Thr Lys Lys Gly Gly Val His Arg Gly Arg Pro Gly Gln Ser Leu Ala
225 230 235 240

Pro Gly Arg Gly

<210> 441
<211> 165
<212> PRT
<213> Homo sapiens

<400> 441
Lys Val Thr Asp Gly His Thr Arg Thr Pro Arg Ser Gly Val Pro Arg
1 5 10 15

Gln His Lys Glu Arg Arg Gly Ser Gln Arg Lys Ala Arg Ala Glu Pro
20 25 30

Gly Pro Arg Glu Gly Met Arg Thr Phe Pro Val Gln Val Ala Ala Gly
35 40 45

Cys Ser Gly Arg Lys Ser His Ala Ser Val Asn Cys Trp Gly Trp Arg
50 55 60

```
Pro Ala Pro Leu Gln Gly Pro Ala Leu Thr Leu His Val Ala Ile Gln
 65                  70                  75                  80

Leu Pro Ser Gly Cys Pro Trp Pro Trp His Arg His Arg Ala Ser Arg
                85                  90                  95

Ala Gly Leu Ala Gly Pro Gly Pro Gly Pro Gly Gly Val Ala Arg Pro
            100                 105                 110

Ile Leu Met Trp Gly Gly Ser Ala Leu His Gly Gly Lys His Ser Lys
        115                 120                 125

His Arg Thr Leu Lys Pro Lys Ala Pro Leu Gly Ser Leu Ala Pro Thr
    130                 135                 140

Ser Trp Gly Gly Asp Arg Arg His Arg Asp Leu Ser Pro Lys Pro Ala
145                 150                 155                 160

Gly Gly Ser Ser Cys
                165
```

<210> 442
<211> 128
<212> PRT
<213> Homo sapiens

<400> 442

```
Met Arg Thr Phe Pro Val Gln Val Ala Ala Gly Cys Ser Gly Arg Lys
  1               5                  10                  15

Ser His Ala Ser Val Asn Cys Trp Gly Trp Arg Pro Ala Pro Leu Gln
            20                  25                  30

Gly Pro Ala Leu Thr Leu His Val Ala Ile Gln Leu Pro Ser Gly Cys
        35                  40                  45

Pro Trp Pro Trp His Arg His Arg Ala Ser Arg Ala Gly Leu Ala Gly
    50                  55                  60

Pro Gly Pro Gly Pro Gly Gly Val Ala Arg Pro Ile Leu Met Trp Gly
 65                  70                  75                  80

Gly Ser Ala Leu His Gly Gly Lys His Ser Lys His Arg Thr Leu Lys
                85                  90                  95

Pro Lys Ala Pro Leu Gly Ser Leu Ala Pro Thr Ser Trp Gly Gly Asp
            100                 105                 110

Arg Arg His Arg Asp Leu Ser Pro Lys Pro Ala Gly Gly Ser Ser Cys
        115                 120                 125
```

<210> 443
<211> 13
<212> PRT
<213> Homo sapiens

<400> 443
Gly Leu Met Glu Cys Leu Ile His Arg His Gly Ser His
1 5 10

<210> 444
<211> 17
<212> PRT
<213> Homo sapiens

<400> 444
Ser Thr Lys Gly Met Gln Phe Ile Leu Thr Gly Ile Thr Leu Ser Gly
1 5 10 15

Tyr

<210> 445
<211> 209
<212> PRT
<213> Homo sapiens

<400> 445
Pro Arg Val Arg Ala Leu Leu Phe Ala Arg Ser Leu Arg Leu Cys Arg
1 5 10 15

Trp Gly Ala Lys Arg Leu Gly Val Ala Ser Thr Glu Ala Gln Arg Gly
20 25 30

Val Ser Phe Lys Leu Glu Glu Lys Thr Ala His Ser Ser Leu Ala Leu
35 40 45

Phe Arg Asp Asp Thr Gly Val Lys Tyr Gly Leu Val Gly Leu Glu Pro
50 55 60

Thr Lys Val Ala Leu Asn Val Glu Arg Phe Arg Glu Trp Ala Val Val
65 70 75 80

Leu Ala Asp Thr Ala Val Thr Ser Gly Arg His Tyr Trp Glu Val Thr
85 90 95

Val Lys Arg Ser Gln Gln Phe Arg Ile Gly Val Ala Asp Val Asp Met
100 105 110

Ser Arg Asp Ser Cys Ile Gly Val Asp Asp Arg Ser Trp Val Phe Thr
115 120 125

Met Pro Ser Ala Ser Gly Thr Pro Cys Trp Pro Thr Arg Lys Pro Gln
130 135 140

Leu Arg Val Leu Gly Ser Gln Glu Val Gly Leu Leu Leu Glu Tyr Glu
145 150 155 160

Ala Gln Lys Leu Ser Leu Val Asp Val Ser Gln Val Ser Val Val His
165 170 175

Thr Leu Gln Thr Asp Phe Arg Gly Pro Val Val Pro Ala Phe Ala Leu
180 185 190

234

Trp Asp Gly Glu Leu Leu Thr His Ser Gly Leu Glu Val Pro Glu Gly
195 200 205

Leu

<210> 446
<211> 98
<212> PRT
<213> Homo sapiens

<400> 446
Met Ser Arg Asp Ser Cys Ile Gly Val Asp Asp Arg Ser Trp Val Phe
1 5 10 15

Thr Met Pro Ser Ala Ser Gly Thr Pro Cys Trp Pro Thr Arg Lys Pro
20 25 30

Gln Leu Arg Val Leu Gly Ser Gln Glu Val Gly Leu Leu Leu Glu Tyr
35 40 45

Glu Ala Gln Lys Leu Ser Leu Val Asp Val Ser Gln Val Ser Val Val
50 55 60

His Thr Leu Gln Thr Asp Phe Arg Gly Pro Val Val Pro Ala Phe Ala
65 70 75 80

Leu Trp Asp Gly Glu Leu Leu Thr His Ser Gly Leu Glu Val Pro Glu
85 90 95

Gly Leu

<210> 447
<211> 1913
<212> DNA
<213> Homo sapiens

<400> 447
GCACGAGCGG CACGAGCGGA TCCTCACACG ACTGTGATCC GATTCTTTCC AGCGGCTTCT 60

GCAACCAAGC GGGTCTTACC CCCGGTCCTC CGCGTCTCCA GTCCTCGCAC CTGGAACCCC 120

AACGTCCCCG AGAGTCCCCG AATCCCCGCT CCCAGGCTAC CTAAGAGGAT GAGCGGTGCT 180

CCGACGGCCG GGGCAGCCCT GATGCTCTGC GCCGCCACCG CCGTGCTACT GAGCGCTCAG 240

GGCGGACCCG TGCAGTCCAA GTCGCCGCGC TTTGCGTCCT GGGACGAGAT GAATGTCCTG 300

GCGCACGGAC TCCTGCAGCT CGGCCAGGGG CTGCGCGAAC ACGCGGAGCG CACCCGCAGT 360

CAGCTGAGCG CGCTGGAGCG GCGCCTGAGC GCGTGCGGGT CCGCCTGTCA GGGAACCGAG 420

GGGTCCACCG ACCTCCCGTT AGCCCCTGAG AGCCGGGTGG ACCCTGAGGT CCTTCACAGC 480

CTGCAGACAC AACTCAAGGC TCAGAACAGC AGGATCCAGC AACTCTTCCA CAAGGTGGCC 540

CAGCAGCAGC GGCACCTGGA GAAGCAGCAC CTGCGAATTC AGCATCTGCA AAGCCAGTTT 600

GGCCTCCTGG ACCACAAGCA CCTAGACCAT GAGGTGGCCA AGCCTGCCCG AAGAAAGAGG 660

CTGCCCGAGA TGGCCCAGCC AGTTGACCCG GCTCACAATG TCAGCCGCCT GCACCGGCTG 720

CCCAGGGATT GCCAGGAGCT GTTCCAGGTT GGGGAGAGGC AGAGTGGACT ATTTGAAATC 780

CAGCCTCAGG GGTCTCCGCC ATTTTTGGTG AACTGCAAGA TGACCTCAGA TGGAGGCTGG 840

ACAGTAATTC AGAGGCGCCA CGATGGCTCA GTGGACTTCA ACCGGCCCTG GGAAGCCTAC 900

AAGGCGGGGT TTGGGGATCC CCACGGCGAG TTCTGGCTGG GTCTGGAGAA GGTGCATAGC 960

ATCACGGGGG ACCGCAACAG CCGCCTGGCC GTGCAGCTGC GGGACTGGGA TGGCAACGCC 1020

GAGTTGCTGC AGTTCTCCGT GCACCTGGGT GGCGAGGACA CGGCCTATAG CCTGCAGCTC 1080

ACTGCACCCG TGGCCGGCCA GCTGGGCGCC ACCACCGTCC CACCCAGCGG CCTCTCCGTA 1140

CCCTTCTCCA CTTGGGACCA GGATCACGAC CTCCGCAGGG ACAAGAACTG CGCCAAGAGC 1200

CTCTCTGGAG GCTGGTGGTT TGGCACCTGC AGCCATTCCA ACCTCAACGG CCAGTACTTC 1260

CGCTCCATCC CACAGCAGCG GCAGAAGCTT AAGAAGGGAA TCTTCTGGAA GACCTGGCGG 1320

GGCCGCTACT ACCCGCTGCA GGCCACCACC ATGTTGATCC AGCCCATGGC AGCAGAGGCA 1380

GCCTCCTAGC GTCCTGGCTG GGCCTGGTCC CAGGCCCACG AAAGACGGTG ACTCTTGGCT 1440

CTGCCCGAGG ATGTGGCCGT TCCCTGCCTG GGCAGGGGCT CCAAGGAGGG GCCATCTGGA 1500

AACTTGTGGA CAGAGAAGAA GACCACGACT GGAGAAGCCC CCTTTCTGAG TGCAGGGGGG 1560

CTGCATGCGT TGCCTCCTGA GATCGAGGCT GCAGGATATG CTCAGACTCT AGAGGCGTGG 1620

ACCAAGGGGC ATGGAGCTTC ACTCCTTGCT GGCCAGGGAG TTGGGGACTC AGAGGGACCA 1680

CTTGGGGCCA GCCAGACTGG CCTCAATGGC GGACTCAGTC ACATTGACTG ACGGGGACCA 1740

GGGCTTGTGT GGGTCGAGAG CGCCCTCATG GTGCTGGTGC TGTTGTGTGT AGGTCCCCTG 1800

GGGACACAAG CAGGCGCCAA TGGTATCTGG GCGGAGCTCA CAGAGTTCTT GGAATAAAAG 1860

CAACCTCAGA ACAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAA 1913

<210> 448
<211> 1221
<212> DNA
<213> Homo sapiens

<400> 448
ATGAGCGGTG CTCCGACGGC CGGGGCAGCC CTGATGCTCT GCGCCGCCAC CGCCGTGCTA 60

CTGAGCGCTC AGGGCGGACC CGTGCAGTCC AAGTCGCCGC GCTTTGCGTC CTGGGACGAG 120

ATGAATGTCC TGGCGCACGG ACTCCTGCAG CTCGGCCAGG GGCTGCGCGA ACACGCGGAG 180

CGCACCCGCA GTCAGCTGAG CGCGCTGGAG CGGCGCCTGA GCGCGTGCGG GTCCGCCTGT 240

CAGGGAACCG AGGGGTCCAC CGACCTCCCG TTAGCCCCTG AGAGCCGGGT GGACCCTGAG 300

GTCCTTCACA GCCTGCAGAC ACAACTCAAG GCTCAGAACA GCAGGATCCA GCAACTCTTC 360

CACAAGGTGG CCCAGCAGCA GCGGCACCTG GAGAAGCAGC ACCTGCGAAT TCAGCATCTG 420

CAAAGCCAGT TTGGCCTCCT GGACCACAAG CACCTAGACC ATGAGGTGGC CAAGCCTGCC 480

CGAAGAAAGA GGCTGCCCGA GATGGCCCAG CCAGTTGACC CGGCTCACAA TGTCAGCCGC 540

CTGCACCGGC TGCCCAGGGA TTGCCAGGAG CTGTTCCAGG TTGGGGAGAG GCAGAGTGGA 600

CTATTTGAAA TCCAGCCTCA GGGGTCTCCG CCATTTTTGG TGAACTGCAA GATGACCTCA 660

GATGGAGGCT GGACAGTAAT TCAGAGGCGC CACGATGGCT CAGTGGACTT CAACCGGCCC 720

TGGGAAGCCT ACAAGGCGGG GTTTGGGGAT CCCCACGGCG AGTTCTGGCT GGGTCTGGAG 780

AAGGTGCATA GCATCACGGG GGACCGCAAC AGCCGCCTGG CCGTGCAGCT GCGGGACTGG 840

GATGGCAACG CCGAGTTGCT GCAGTTCTCC GTGCACCTGG GTGGCGAGGA CACGGCCTAT 900

AGCCTGCAGC TCACTGCACC CGTGGCCGGC CAGCTGGGCG CCACCACCGT CCCACCCAGC 960

GGCCTCTCCG TACCCTTCTC CACTTGGGAC CAGGATCACG ACCTCCGCAG GGACAAGAAC 1020

TGCGCCAAGA GCCTCTCTGG AGGCTGGTGG TTTGGCACCT GCAGCCATTC CAACCTCAAC 1080

GGCCAGTACT TCCGCTCCAT CCCACAGCAG CGGCAGAAGC TTAAGAAGGG AATCTTCTGG 1140

AAGACCTGGC GGGGCCGCTA CTACCCGCTG CAGGCCACCA CCATGTTGAT CCAGCCCATG 1200

GCAGCAGAGG CAGCCTCCTA G 1221

<210> 449
<211> 175
<212> PRT
<213> Homo sapiens

<400> 449
Met Ala Gln Trp Thr Ser Thr Gly Pro Gly Lys Pro Thr Arg Arg Gly
1 5 10 15

Leu Gly Ile Pro Thr Ala Ser Ser Gly Trp Val Trp Arg Arg Cys Ile
20 25 30

Ala Ser Trp Gly Thr Ala Thr Ala Ala Trp Pro Cys Ser Cys Gly Thr
35 40 45

Gly Met Ala Thr Pro Ser Cys Cys Ser Ser Pro Cys Thr Trp Val Ala
50 55 60

Arg Thr Arg Pro Ile Ala Cys Ser Ser Leu His Pro Trp Pro Ala Ser
65 70 75 80

Trp Ala Pro Pro Pro Ser His Pro Ala Ala Ser Pro Tyr Pro Ser Pro
85 90 95

Leu Gly Thr Arg Ile Thr Thr Ser Ala Gly Thr Arg Thr Ala Pro Arg
100 105 110

Ala Ser Leu Glu Ala Gly Gly Leu Ala Pro Ala Ala Ile Pro Thr Phe
115 120 125

Asn Gly Pro Val Leu Pro Ala Pro Ser His Ser Ser Gly Arg Ser Leu
130 135 140

Arg Arg Glu Ser Ser Gly Arg Pro Ala Gly Arg Tyr Tyr Pro Leu Gln
145 150 155 160

Ala Thr Thr Met Leu Ile Gln Pro Met Ala Ala Glu Ala Ala Ser
165 170 175

<210> 450
<211> 32
<212> PRT
<213> Homo sapiens

<400> 450
Gly His Asp Leu Pro Gln Asp Ala Trp Leu Arg Trp Val Leu Ala Gly
1 5 10 15

Ala Leu Cys Ala Gly Gly Trp Ala Val Asn Tyr Leu Pro Phe Phe Leu
20 25 30

<210> 451
<211> 18
<212> PRT
<213> Homo sapiens

<400> 451
Phe Leu Tyr His Tyr Leu Pro Ala Leu Thr Phe Gln Ile Leu Leu Leu
1 5 10 15

Pro Val

<210> 452
<211> 59
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (44)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (49)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 452
Met Ser Pro Leu Pro Trp Pro Gly Pro Leu Pro Gly Gly Arg Gln Gly

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 1               5                  10                  15

His Arg Leu Glu Pro Cys Cys Ser Ser Gly Cys Ala Gly Gly Pro Thr
            20                  25                  30

Trp Pro His Cys Ser Ser Gln Ser Trp Pro Met Xaa Ser Ala Arg His
        35                  40                  45

Xaa Gly Leu Gly His Cys Cys Pro Ser Ser Pro
    50                  55

<210> 453
<211> 32
<212> PRT
<213> Homo sapiens

<400> 453
Asp Ile Cys Arg Leu Glu Arg Ala Val Cys Arg Asp Glu Pro Ser Ala
 1               5                  10                  15

Leu Ala Arg Ala Leu Thr Trp Arg Gln Ala Arg Ala Gln Ala Gly Ala
            20                  25                  30

<210> 454
<211> 114
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (1)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (6)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 454
Xaa Ala Pro Ala Thr Xaa Ala Trp Asp Thr Val Val Pro Pro Leu Pro
 1               5                  10                  15

Arg Lys Cys Gln Cys Ser Gly Ser Ala Arg Ser His Gly Ala Gly Arg
            20                  25                  30

Ser Ala Leu His Ser Pro Leu Glu Gly Ser Arg Pro Lys Val Pro Ala
        35                  40                  45

Gly Ala Val Gly Lys Ser Leu Pro Gly Gln Ser Arg Pro Gln His Cys
    50                  55                  60

Leu Pro Pro Lys Gln Pro Lys Gln Cys Arg Pro Gly Leu Glu Leu Lys
65                  70                  75                  80

Glu Gly Pro Leu Leu Thr Pro Thr Arg Ala Ser Val Gln Leu Ser His
                85                  90                  95
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Pro Ala Cys Leu Tyr Trp Ala Pro Leu Leu Trp Ile Arg Asp Pro Ala
100 105 110

Ser Val

<210> 455
<211> 55
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (1)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (6)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 455
Xaa Ala Pro Ala Thr Xaa Ala Trp Asp Thr Val Val Pro Pro Leu Pro
1 5 10 15

Arg Lys Cys Gln Cys Ser Gly Ser Ala Arg Ser His Gly Ala Gly Arg
20 25 30

Ser Ala Leu His Ser Pro Leu Glu Gly Ser Arg Pro Lys Val Pro Ala
35 40 45

Gly Ala Val Gly Lys Ser Leu
50 55

<210> 456
<211> 59
<212> PRT
<213> Homo sapiens

<400> 456
Pro Gly Gln Ser Arg Pro Gln His Cys Leu Pro Pro Lys Gln Pro Lys
1 5 10 15

Gln Cys Arg Pro Gly Leu Glu Leu Lys Glu Gly Pro Leu Leu Thr Pro
20 25 30

Thr Arg Ala Ser Val Gln Leu Ser His Pro Ala Cys Leu Tyr Trp Ala
35 40 45

Pro Leu Leu Trp Ile Arg Asp Pro Ala Ser Val
50 55

<210> 457
<211> 133
<212> PRT
<213> Homo sapiens

<220>

<221> SITE
<222> (55)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (61)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 457
Asp Ile Cys Arg Leu Glu Arg Ala Val Cys Arg Asp Glu Pro Ser Ala
1 5 10 15

Leu Ala Arg Ala Leu Thr Trp Arg Gln Ala Arg Ala Gln Ala Gly Ala
20 25 30

Met Leu Leu Phe Gly Leu Cys Trp Gly Pro Tyr Val Ala Thr Leu Leu
35 40 45

Leu Ser Val Leu Ala Tyr Xaa Gln Arg Pro Pro Leu Xaa Pro Gly Thr
50 55 60

Leu Leu Ser Leu Leu Ser Leu Gly Ser Ala Ser Ala Ala Ala Val Pro
65 70 75 80

Val Ala Met Gly Leu Gly Asp Gln Arg Tyr Thr Ala Pro Trp Arg Ala
85 90 95

Ala Ala Gln Arg Cys Leu Gln Gly Leu Trp Gly Arg Ala Ser Arg Asp
100 105 110

Ser Pro Gly Pro Ser Ile Ala Tyr His Pro Ser Ser Gln Ser Ser Val
115 120 125

Asp Leu Asp Leu Asn
130

<210> 458
<211> 48
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (34)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (43)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 458
Met Glu Arg Val Gly Met Glu Ser Gly Glu Met Val Cys Gly Leu Gly
1 5 10 15

Ser Ala Cys Asn Asn Pro Ser Asp Leu Gly Gln Val Pro Val Pro Leu
20 25 30

Trp Xaa Ser Val Ser Pro Pro Val Phe Gly Xaa Gly Trp Asn Gly His
35 40 45

<210> 459
<211> 107
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (84)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 459
Met Arg Ser Phe Gln Asp Val Ser Ala Leu Glu Glu Trp Arg Gly Gly
1 5 10 15

Lys Asp Leu Glu Pro Thr His Ser Leu Leu Leu Leu Leu Pro Leu Arg
20 25 30

Asp Leu Leu Val Val Leu Gly Glu Ile Arg Lys Arg Gln Met Glu Gly
35 40 45

Cys Val Trp Lys Gly Trp Gly Trp Asn Pro Glu Lys Trp Phe Ala Val
50 55 60

Leu Ala Leu Pro Val Thr Thr Arg Val Thr Leu Gly Lys Ser Leu Ser
65 70 75 80

Leu Ser Gly Xaa Gln Phe Leu His Leu Tyr Leu Glu Arg Val Gly Met
85 90 95

Gly Thr Glu Val Leu Ser Ser Ser Asp Leu Leu
100 105

<210> 460
<211> 118
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (62)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (70)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 460
Met His Pro Ala Gly Pro Thr Phe Met Gly Ser Lys Pro Ile Arg Glu
1 5 10 15

Gln Gln Phe Gly Pro Asp Ala Cys Leu Leu Leu Leu Cys Val Ala Met
20 25 30

Ala Gly Thr Glu Ala Ser Arg Ala Ala Gln Gln Cys Thr Ser Gln Lys
35 40 45

Val Arg Ala Gly Gln Asp Phe Ser Ala His Ser Asn Pro Xaa Gln Ile
50 55 60

Gln Val Glu Lys Leu Xaa Pro Arg Glu Gly Gln Gly Leu Ala Gln Gly
65 70 75 80

His Ser Gly Cys Tyr Arg Gln Ser Gln Asp Arg Lys Pro Phe Leu Arg
85 90 95

Ile Pro Ser Pro Pro Phe Pro Tyr Thr Thr Leu His Leu Pro Phe Pro
100 105 110

Asp Phe Ala Lys Asn His
115

<210> 461
<211> 61
<212> PRT
<213> Homo sapiens

<400> 461
Met His Pro Ala Gly Pro Thr Phe Met Gly Ser Lys Pro Ile Arg Glu
1 5 10 15

Gln Gln Phe Gly Pro Asp Ala Cys Leu Leu Leu Leu Cys Val Ala Met
20 25 30

Ala Gly Thr Glu Ala Ser Arg Ala Ala Gln Gln Cys Thr Ser Gln Lys
35 40 45

Val Arg Ala Gly Gln Asp Phe Ser Ala His Ser Asn Pro
50 55 60

<210> 462
<211> 48
<212> PRT
<213> Homo sapiens

<400> 462
Pro Arg Glu Gly Gln Gly Leu Ala Gln Gly His Ser Gly Cys Tyr Arg
1 5 10 15

Gln Ser Gln Asp Arg Lys Pro Phe Leu Arg Ile Pro Ser Pro Pro Phe
20 25 30

Pro Tyr Thr Thr Leu His Leu Pro Phe Pro Asp Phe Ala Lys Asn His
35 40 45

<210> 463
<211> 22
<212> PRT
<213> Homo sapiens

<400> 463
Asp Pro Arg Val Arg Lys Pro Pro Thr Ala Thr Leu Thr Thr Ala Arg
1 5 10 15

Thr Arg Pro Thr Thr Asp
20

<210> 464
<211> 82
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (70)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (81)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (82)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 464
Ala Ala Leu Glu Ala Ser Val Pro Ala Ile Ala Thr Gln Arg Ser Ser
1 5 10 15

Arg Gln Ala Ser Gly Pro Asn Cys Cys Ser Leu Met Gly Leu Asp Pro
20 25 30

Met Lys Val Gly Pro Ala Gly Cys Ile Ser Trp Asp Ser Val Glu Ala
35 40 45

Asp Gln Val Ala Gly Ala Ser Gly Gly Arg Ile Glu Val Lys Gly Cys
50 55 60

Gly Met Glu Asn Leu Xaa Arg Leu His Leu Gly Ser Gly Lys Gly Gln
65 70 75 80

Xaa Xaa

<210> 465
<211> 99
<212> PRT
<213> Homo sapiens

<400> 465
Met Leu His Arg Gln Trp Leu Thr Val Arg Arg Ala Gly Gly Pro Pro
1 5 10 15

Arg Thr Asp Gln Gln Arg Arg Thr Val Arg Cys Leu Arg Asp Thr Val
20 25 30

Leu Leu Leu His Gly Leu Ser Gln Lys Asp Lys Leu Phe Met Met His
35 40 45

Cys Val Glu Val Leu His Gln Phe Asp Gln Val Met Pro Gly Val Ser
50 55 60

Met Leu Ile Arg Gly Leu Pro Asp Val Thr Asp Cys Glu Glu Ala Ala
65 70 75 80

Leu Asp Asp Leu Cys Ala Ala Glu Thr Asp Val Glu Asp Pro Glu Val
85 90 95

Glu Cys Gly

<210> 466
<211> 62
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (2)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (58)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 466
Gly Xaa Ala Asn Pro Glu Asp Ser Val Cys Ile Leu Glu Gly Phe Ser
1 5 10 15

Val Thr Ala Leu Ser Ile Leu Gln His Leu Val Cys His Ser Gly Ala
20 25 30

Val Arg Leu Pro Ile Thr Val Arg Ser Gly Gly Arg Phe Cys Cys Trp
35 40 45

Gly Arg Lys Gln Glu Pro Gly Ser Gln Xaa Ser Asp Gly Asp
50 55 60

<210> 467
<211> 65
<212> PRT
<213> Homo sapiens

<400> 467
Ala Val Gln Gln Gln His Arg Val Pro Gln Thr Ala His Cys Pro Pro
1 5 10 15

Leu Leu Val Gly Pro Trp Gly Ser Pro Cys Pro Pro His Cys Gln Pro
20 25 30

Leu Ser Val Gln His His Arg Glu Arg Ser Asp His Leu His Ile Thr
35 40 45

Leu Ala Val Gly Ala Ser Asp Trp Gly Gln Gly Ala Leu Ala His Gln

245

50 55 60

Ala
65

<210> 468
<211> 220
<212> PRT
<213> Homo sapiens

<400> 468
Pro Lys Thr Leu Pro Val Ile Ser Cys Pro Gly Ser Ser Val Cys Ser
1 5 10 15

Lys Cys Cys Gln Ser Ala Ser Ala Gln Arg His Pro Cys Leu Ala Cys
20 25 30

Cys Trp Leu Leu Ser Ser Ser Pro Cys Trp Arg Thr Thr Thr Ser Trp
35 40 45

His Leu Ser Ser Val Pro Thr Gln Lys Ala Ala Ser Cys Cys Cys Cys
50 55 60

Thr Cys Thr Ser His His Gly Leu Thr Glu Trp Pro Trp Arg His Asn
65 70 75 80

Gly Ser Ser Trp Asn Lys Arg Trp Cys Gly Ser Trp Leu Ser Leu Val
85 90 95

Cys Lys Ser Pro Leu Pro Pro Val Thr Gly Ser Asn Cys Gln Cys Asn
100 105 110

Val Glu Val Val Arg Ala Leu Thr Val Met Leu His Arg Gln Trp Leu
115 120 125

Thr Val Arg Arg Ala Gly Gly Pro Pro Arg Thr Asp Gln Gln Arg Arg
130 135 140

Thr Val Arg Cys Leu Arg Asp Thr Val Leu Leu Leu His Gly Leu Ser
145 150 155 160

Gln Lys Asp Lys Leu Phe Met Met His Cys Val Glu Val Leu His Gln
165 170 175

Phe Asp Gln Val Met Pro Gly Val Ser Met Leu Ile Arg Gly Leu Pro
180 185 190

Asp Val Thr Asp Cys Glu Glu Ala Ala Leu Asp Asp Leu Cys Ala Ala
195 200 205

Glu Thr Asp Val Glu Asp Pro Glu Val Glu Cys Gly
210 215 220

<210> 469
<211> 223
<212> PRT
<213> Homo sapiens

<220>

<221> SITE
<222> (2)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (58)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 469
Gly Xaa Ala Asn Pro Glu Asp Ser Val Cys Ile Leu Glu Gly Phe Ser
1 5 10 15

Val Thr Ala Leu Ser Ile Leu Gln His Leu Val Cys His Ser Gly Ala
20 25 30

Val Arg Leu Pro Ile Thr Val Arg Ser Gly Gly Arg Phe Cys Cys Trp
35 40 45

Gly Arg Lys Gln Glu Pro Gly Ser Gln Xaa Ser Asp Gly Asp Met Thr
50 55 60

Ser Ala Leu Arg Gly Val Ala Asp Asp Gln Gly Gln His Pro Leu Leu
65 70 75 80

Lys Met Leu Leu His Leu Leu Ala Phe Ser Ser Ala Ala Thr Gly His
85 90 95

Leu Gln Ala Ser Val Leu Thr Gln Cys Leu Lys Val Leu Val Lys Leu
100 105 110

Ala Glu Asn Thr Ser Cys Asp Phe Leu Pro Arg Phe Gln Cys Val Phe
115 120 125

Gln Val Leu Pro Lys Cys Leu Ser Pro Glu Thr Pro Leu Pro Ser Val
130 135 140

Leu Leu Ala Val Glu Leu Leu Ser Leu Leu Ala Asp His Asp Gln Leu
145 150 155 160

Ala Pro Gln Leu Cys Ser His Ser Glu Gly Cys Leu Leu Leu Leu Leu
165 170 175

Tyr Met Tyr Ile Thr Ser Arg Pro Asp Arg Val Ala Leu Glu Thr Gln
180 185 190

Trp Leu Gln Leu Glu Gln Glu Val Val Trp Leu Leu Ala Lys Leu Gly
195 200 205

Val Gln Glu Pro Leu Ala Pro Ser His Trp Leu Gln Leu Pro Val
210 215 220

<210> 470
<211> 102
<212> PRT
<213> Homo sapiens

<400> 470
Met Ser Gly Gln Leu Asp Ala Arg Pro Ala Ala Ala Leu His Pro Gln

247

1 5 10 15

Gly Leu Ala His Pro Leu Trp Thr Cys Leu Leu Pro Arg Lys Gly Pro
20 25 30

Ser Glu Val Pro Gln Arg Pro Pro Gln Leu Trp Val Val Ser Ile Ser
35 40 45

Val Leu Gln Gly Gln His Arg Gly Arg Ala Gly Pro Arg Asp Glu Gln
50 55 60

Ser Val Asp Val Thr Asn Thr Thr Phe Leu Leu Met Ala Ala Ser Ile
65 70 75 80

Tyr Leu His Asp Gln Asn Pro Asp Ala Ala Leu Arg Ala Leu His Gln
85 90 95

Gly Asp Ser Leu Glu Trp
100

<210> 471
<211> 20
<212> PRT
<213> Homo sapiens

<400> 471
Ser Val Asp Val Thr Asn Thr Thr Phe Leu Leu Met Ala Ala Ser Ile
1 5 10 15

Tyr Leu His Asp
20

<210> 472
<211> 17
<212> PRT
<213> Homo sapiens

<400> 472
Gln Asn Pro Asp Ala Ala Leu Arg Ala Leu His Gln Gly Asp Ser Leu
1 5 10 15

Glu

<210> 473
<211> 14
<212> PRT
<213> Homo sapiens

<400> 473
Arg Asp Ser Ile Val Ala Glu Leu Asp Arg Glu Met Ser Arg
1 5 10

<210> 474
<211> 39
<212> PRT
<213> Homo sapiens

<400> 474

Met Leu Gly Leu Leu Leu Leu Cys Thr Pro Arg Ala Trp Leu Thr Leu
1 5 10 15

Ser Gly Pro Val Cys Phe Gln Gly Arg Asp Pro Leu Arg Ser His Arg
20 25 30

Gly His Pro Ser Cys Gly Ser
35

<210> 475
<211> 11
<212> PRT
<213> Homo sapiens

<400> 475
His Gly Phe Pro Glu Phe Trp Tyr Ser Trp Arg
1 5 10

<210> 476
<211> 10
<212> PRT
<213> Homo sapiens

<400> 476
Ala Ser His Trp Leu Gln Gln Asp Gln Pro
1 5 10

<210> 477
<211> 9
<212> PRT
<213> Homo sapiens

<400> 477
Pro Ile Asn His Tyr Arg Asn Ile Phe
1 5

<210> 478
<211> 9
<212> PRT
<213> Homo sapiens

<400> 478
Tyr Pro Glu Met Val Met Lys Leu Ile
1 5

<210> 479
<211> 14
<212> PRT
<213> Homo sapiens

<400> 479
Pro Glu Phe Trp Tyr Ser Trp Arg Tyr Gln Leu Arg Glu Phe
1 5 10

<210> 480
<211> 9
<212> PRT
<213> Homo sapiens

<400> 480
His Asp Trp Gly Gly Met Ile Ala Trp
1 5

<210> 481
<211> 14
<212> PRT
<213> Homo sapiens

<400> 481
Gly Ser Leu Pro Pro Lys Pro Ile Tyr Leu Val Val Pro Arg
1 5 10

<210> 482
<211> 16
<212> PRT
<213> Homo sapiens

<400> 482
Leu Val Phe Ala Glu His Arg Tyr Tyr Gly Lys Ser Leu Pro Phe Gly
1 5 10 15

<210> 483
<211> 10
<212> PRT
<213> Homo sapiens

<400> 483
Glu Gln Ala Leu Ala Asp Phe Ala Glu Leu
1 5 10

<210> 484
<211> 18
<212> PRT
<213> Homo sapiens

<400> 484
Gly Gly Ser Tyr Gly Gly Met Leu Ser Ala Tyr Leu Arg Met Lys Tyr
1 5 10 15

Pro His

<210> 485
<211> 16
<212> PRT
<213> Homo sapiens

<400> 485
Asn Ile Ile Phe Ser Asn Gly Asn Leu Asp Pro Trp Ala Gly Gly Gly
1 5 10 15

<210> 486

250

<211> 22
<212> PRT
<213> Homo sapiens

<400> 486
Ala Met Met Asp Tyr Pro Tyr Pro Thr Asp Phe Leu Gly Pro Leu Pro
1 5 10 15

Ala Asn Pro Val Lys Val
20

<210> 487
<211> 8
<212> PRT
<213> Homo sapiens

<400> 487
Phe Tyr Thr Gly Asn Glu Gly Asp
1 5

<210> 488
<211> 490
<212> PRT
<213> Homo sapiens

<400> 488
Met Gly Ser Ala Pro Trp Ala Pro Val Leu Leu Leu Ala Leu Gly Leu
1 5 10 15

Arg Gly Leu Gln Ala Gly Ala Arg Ser Gly Pro Arg Leu Pro Gly Ala
20 25 30

Leu Leu Pro Ala Ala Ser Gly Pro Leu Gln Leu Arg Ala Leu Arg Gln
35 40 45

Gln Asp Leu Pro Ser Ala Leu Pro Gly Val Gly Gln Val Leu Gly Pro
50 55 60

Gly Arg Gly Ala His Leu Leu Leu His Trp Glu Arg Gly Arg Arg Val
65 70 75 80

Gly Leu Arg Gln Gln Leu Gly Leu Arg Arg Gly Leu Ala Ala Glu Arg
85 90 95

Gly Ala Leu Leu Val Phe Ala Glu His Arg Tyr Tyr Gly Lys Ser Leu
100 105 110

Pro Phe Gly Ala Gln Ser Thr Gln Arg Gly His Thr Glu Leu Leu Thr
115 120 125

Val Glu Gln Ala Leu Ala Asp Phe Ala Glu Leu Leu Arg Ala Leu Arg
130 135 140

Arg Asp Leu Gly Ala Gln Asp Ala Pro Ala Ile Ala Phe Gly Gly Ser
145 150 155 160

Tyr Gly Gly Met Leu Ser Ala Tyr Leu Arg Met Lys Tyr Pro His Leu
165 170 175

Val Ala Gly Ala Leu Ala Ala Ser Ala Pro Val Leu Ser Val Ala Gly
180 185 190

Leu Gly Asp Ser Asn Gln Phe Phe Arg Asp Val Thr Ala Asp Phe Glu
195 200 205

Gly Gln Ser Pro Lys Cys Thr Gln Gly Val Arg Glu Ala Phe Arg Gln
210 215 220

Ile Lys Asp Leu Phe Leu Gln Gly Ala Tyr Asp Thr Val Arg Trp Glu
225 230 235 240

Phe Gly Thr Cys Gln Pro Leu Ser Asp Glu Lys Asp Leu Thr Gln Leu
245 250 255

Phe Met Phe Ala Arg Asn Ala Phe Thr Val Leu Ala Met Met Asp Tyr
260 265 270

Pro Tyr Pro Thr Asp Phe Leu Gly Pro Leu Pro Ala Asn Pro Val Lys
275 280 285

Val Gly Cys Asp Arg Leu Leu Ser Glu Ala Gln Arg Ile Thr Gly Leu
290 295 300

Arg Ala Leu Ala Gly Leu Val Tyr Asn Ala Ser Gly Ser Glu His Cys
305 310 315 320

Tyr Asp Ile Tyr Arg Leu Tyr His Ser Cys Ala Asp Pro Thr Gly Cys
325 330 335

Gly Thr Gly Pro Asp Ala Arg Ala Trp Asp Tyr Gln Ala Cys Thr Glu
340 345 350

Ile Asn Leu Thr Phe Ala Ser Asn Asn Val Thr Asp Met Phe Pro Asp
355 360 365

Leu Pro Phe Thr Asp Glu Leu Arg Gln Arg Tyr Cys Leu Asp Thr Trp
370 375 380

Gly Val Trp Pro Arg Pro Asp Trp Leu Leu Thr Ser Phe Trp Gly Gly
385 390 395 400

Asp Leu Arg Ala Ala Ser Asn Ile Ile Phe Ser Asn Gly Asn Leu Asp
405 410 415

Pro Trp Ala Gly Gly Gly Ile Arg Arg Asn Leu Ser Ala Ser Val Ile
420 425 430

Ala Val Thr Ile Gln Gly Gly Ala His His Leu Asp Leu Arg Ala Ser
435 440 445

His Pro Glu Asp Pro Ala Ser Val Val Glu Ala Arg Lys Leu Glu Ala
450 455 460

Thr Ile Ile Gly Glu Trp Val Lys Ala Ala Arg Arg Glu Gln Gln Pro
465 470 475 480

Ala Leu Arg Gly Gly Pro Arg Leu Ser Leu
485 490

<210> 489
<211> 22
<212> PRT
<213> Homo sapiens

<400> 489
Cys Ser Val Phe Pro Pro Ser Leu Trp Phe Tyr Leu Pro Leu Val Phe
1 5 10 15

Asp Asp Gly Asp Val Gln
20

<210> 490
<211> 122
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (46)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (113)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 490
Gly Val Ser Leu Pro Leu Leu Gly Asp Ala Ser Gln Leu Gly Tyr Leu
1 5 10 15

Gly Val Arg Asp Ala Leu Glu Glu Ala Leu Cys Leu Phe Ser Asp Val
20 25 30

Gln Leu Cys Ala Gly Arg Thr Ser Ala Leu Phe Lys Ala Xaa Arg Gln
35 40 45

Gly Arg Leu Ser Leu Gln Arg Ile Leu Leu Pro Phe Val Trp Leu Cys
50 55 60

Pro Ala Pro Gln Arg Trp Ser Leu Gln Arg Gln Ala Gly Leu Leu Glu
65 70 75 80

Leu Arg Trp Ala Pro Pro Ser Ser Ser Phe Leu Ala Ala Leu Phe Thr
85 90 95

Pro Ser Ser Leu Gly Asn Gly Gly Arg Pro Ser Pro Ser Leu Thr Ala
100 105 110

Xaa Leu Gln Phe Asp Leu Arg Leu Leu Cys
115 120

<210> 491
<211> 74
<212> PRT
<213> Homo sapiens

<220>

<221> SITE
<222> (62)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (74)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 491
Val Cys Arg Gly Phe Cys Cys Leu Leu Phe Gly Cys Ala Leu Pro Pro
1 5 10 15

Arg Gly Gly Val Tyr Arg Gly Arg Gln Ala Ser Leu Asn Cys Gly Gly
20 25 30

Leu His Arg Val Arg Val Ser Trp Pro Leu Cys Leu Pro Pro Gln Ala
35 40 45

Ser Ala Met Val Gly Ala Pro Pro Pro Ala Ser Leu Pro Xaa Cys Ser
50 55 60

Leu Ile Ser Asp Cys Cys Ala Ser Asn Xaa
65 70

<210> 492
<211> 34
<212> PRT
<213> Homo sapiens

<400> 492
Met Ser His Lys His Met Arg Arg Ser Ala Thr Ser Tyr Ile Ile Arg
1 5 10 15

Glu Arg Gln Ile Lys Ile Ile Val Arg Tyr His Tyr Thr Pro Ile Met
20 25 30

Thr Thr

<210> 493
<211> 16
<212> PRT
<213> Homo sapiens

<400> 493
Ile Arg Glu Arg Gln Ile Lys Ile Ile Val Arg Tyr His Tyr Thr Pro
1 5 10 15

<210> 494
<211> 13
<212> PRT
<213> Homo sapiens

<400> 494
Lys Lys Thr Cys Thr Met Phe Ile Ala Thr Leu Phe Thr

1 5 10

<210> 495
<211> 13
<212> PRT
<213> Homo sapiens

<400> 495
Glu Lys Ile Phe Ala Lys His Leu Ser Val Lys Gly Leu
1 5 10

<210> 496
<211> 85
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (21)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (39)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 496
Ser Val Ala Ser Val Phe Ile Pro Leu Lys Val Ser Val Thr Lys Gln
1 5 10 15

Phe Ile Phe Phe Xaa Phe Phe Phe Phe Leu Arg Arg Ser Leu Ala Pro
20 25 30

Ala Trp Val Ala Glu Arg Xaa Thr Ser Gln Glu Thr Lys Gln Asn Lys
35 40 45

Lys Thr Pro Gln Leu Arg Gly Lys Val Ala His Ala Cys Asp Pro Ile
50 55 60

Thr Leu Gly Gly Arg Arg Trp Glu Val Gly Glu Ser Leu Glu Ala Arg
65 70 75 80

Ser Pro Ser Xaa Xaa
85

<210> 497
<211> 184
<212> PRT
<213> Homo sapiens

<400> 497
Tyr Met Cys Cys Pro Phe Val Leu Asp Lys Asp Gly Val Ser Ala Ala
1 5 10 15

Val Ile Ser Ala Glu Leu Ala Ser Phe Leu Ala Thr Lys Asn Leu Ser
20 25 30

Leu Ser Gln Gln Leu Lys Ala Ile Tyr Val Glu Tyr Gly Tyr His Ile
35 40 45

Thr Lys Ala Ser Tyr Phe Ile Cys His Asp Gln Glu Thr Ile Lys Lys
50 55 60

Leu Phe Glu Asn Leu Arg Asn Tyr Asp Gly Lys Asn Asn Tyr Pro Lys
65 70 75 80

Ala Cys Gly Lys Phe Glu Ile Ser Ala Ile Arg Asp Leu Thr Thr Gly
85 90 95

Tyr Asp Asp Ser Gln Pro Asp Lys Lys Ala Val Leu Pro Thr Ser Lys
100 105 110

Ser Ser Gln Met Ile Thr Phe Thr Phe Ala Asn Gly Gly Val Ala Thr
115 120 125

Met Arg Thr Ser Gly Thr Glu Pro Lys Ile Lys Tyr Tyr Ala Glu Leu
130 135 140

Cys Ala Pro Pro Gly Asn Ser Asp Pro Glu Gln Leu Lys Lys Glu Leu
145 150 155 160

Asn Glu Leu Val Ser Ala Ile Glu Glu His Phe Phe Gln Pro Gln Lys
165 170 175

Tyr Asn Leu Gln Pro Lys Ala Asp
180

<210> 498
<211> 199
<212> PRT
<213> Homo sapiens

<400> 498
Ala Arg Gly Lys Thr Val Leu Phe Ala Phe Glu Glu Ala Ile Gly Tyr
1 5 10 15

Met Cys Cys Pro Phe Val Leu Asp Lys Asp Gly Val Ser Ala Ala Val
20 25 30

Ile Ser Ala Glu Leu Ala Ser Phe Leu Ala Thr Lys Asn Leu Ser Leu
35 40 45

Ser Gln Gln Leu Lys Ala Ile Tyr Val Glu Tyr Gly Tyr His Ile Thr
50 55 60

Lys Ala Ser Tyr Phe Ile Cys His Asp Gln Glu Thr Ile Lys Lys Leu
65 70 75 80

Phe Glu Asn Leu Arg Asn Tyr Asp Gly Lys Asn Asn Tyr Pro Lys Ala
85 90 95

Cys Gly Lys Phe Glu Ile Ser Ala Ile Arg Asp Leu Thr Thr Gly Tyr
100 105 110

Asp Asp Ser Gln Pro Asp Lys Lys Ala Val Leu Pro Thr Ser Lys Ser
115 120 125

Ser Gln Met Ile Thr Phe Thr Phe Ala Asn Gly Gly Val Ala Thr Met

256

130 135 140

Arg Thr Ser Gly Thr Glu Pro Lys Ile Lys Tyr Tyr Ala Glu Leu Cys
145 150 155 160

Ala Pro Pro Gly Asn Ser Asp Pro Glu Gln Leu Lys Lys Glu Leu Asn
165 170 175

Glu Leu Val Ser Ala Ile Glu Glu His Phe Phe Gln Pro Gln Lys Tyr
180 185 190

Asn Leu Gln Pro Lys Ala Asp
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<210> 499
<211> 18
<212> PRT
<213> Homo sapiens

<400> 499
Asp Lys Asp Gly Val Ser Ala Ala Val Ile Ser Ala Glu Leu Ala Ser
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Phe Leu

<210> 500
<211> 13
<212> PRT
<213> Homo sapiens

<400> 500
Arg Asp Leu Thr Thr Gly Tyr Asp Asp Ser Gln Pro Asp
1 5 10

<210> 501
<211> 15
<212> PRT
<213> Homo sapiens

<400> 501
Lys Ala Val Leu Pro Thr Ser Lys Ser Ser Gln Met Ile Thr Phe
1 5 10 15

<210> 502
<211> 17
<212> PRT
<213> Homo sapiens

<400> 502
Thr Met Arg Thr Ser Gly Thr Glu Pro Lys Ile Lys Tyr Tyr Ala Glu
1 5 10 15

Leu

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description
on page 199 , line N/A

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☐

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
August 28, 1997	209226

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the International Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

For receiving Office use only

☑ This sheet was received with the international application

Elnora Rivera
Authorized PCT Operations - IAPD Team 1
(703) 305-3678 (703) 305-3230 (FAX)

For International Bureau use only

☐ This sheet was received by the International Bureau on:

Authorized officer

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 201, line N/A

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☐

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
May 7, 1998	209852

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the International Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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Authorized officer Elnora Rivera PCT Operations - IAPD Team 1 (703) 305-3678 (703) 305-3230 (FAX)	Authorized officer

Form PCT/RO/134 (July 1992)

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 204, line N/A

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☐

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
May 7, 1998	209853

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the International Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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Authorized officer Elnora Rivera PCT Operations - IAPD Team 1 (703) 305-3670 (703) 305-3230 (FAX)	Authorized officer

Form PCT/RO/134 (July 1992)

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM (PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 200, line N/A

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☐

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
March 13, 1997	97958

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the International Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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Elnora Rivera Authorized officer PCT Operations - IAPD Team 1 (703) 305-3678 (703) 305-3230 (FAX)	Authorized officer

Form PCT/RO/134 (July 1992)

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 198, line N/A

B. **IDENTIFICATION OF DEPOSIT** Further deposits are identified on an additional sheet ☐

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
April 20, 1998	209782

C. **ADDITIONAL INDICATIONS** *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. **DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** *(if the indications are not for all designated States)*

Europe
In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).

E. **SEPARATE FURNISHING OF INDICATIONS** *(leave blank if not applicable)*

The indications listed below will be submitted to the International Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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Authorized officer: Elnora Rivera, PCT Operations - IAPD Team 1, (703) 305-3678 (703) 305-3230 (FAX)	Authorized officer

Form PCT/RO/134 (July 1992)

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/13418

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C12N 15/12, 15/63, 1/21, 5/00; C07K 7/00, 14/435

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/69.1, 69.3, 70.1, 325, 243, 320.1; 530/300, 350, 399; 536/23.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, MEDLINE, EMBASE, WPIDS. BIOSIS
search terms: secreted protein, antigenic, antigen

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JACOBS et al. A genetic selection for isolating cDNAs encoding secreted proteins. Gene. 1997, Vol. 198, pages 289-296.	1-12, 14-16, 21
X	US 5,534,409 A (GRONER et al) 09 July 1996, columns 21-26, especially see SEQ ID NO:2.	1-3, 7-11, 14-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
02 SEPTEMBER 1999	29 OCT 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer CHRISTINE SAOUD Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/13418

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-12, 14-16 and 21 with regard to SEQ ID NO:11, 130

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/13418

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

435/69.1, 69.3, 70.1, 325, 243, 320.1; 530/300, 350, 399; 536/23.1

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s)1-12, 14-16 and 21, drawn to polynucleotides, polypeptides, and recombinant methods of production.
Group II, claim(s) 13, drawn to an antibody.
Group III, claim(s) 17, drawn to methods of treatment by administering the polypeptide.
Group IV, claim(s) 17, drawn to methods of treatment by administering the polynucleotides.
Group V, claim(s) 18, drawn to methods of diagnosing by detecting the polynucleotide.
Group VI, claim(s) 19, drawn to methods of diagnosing by detecting the polypeptide.
Group VII, claim(s) 20, drawn to methods of determining a binding partner.
Group VIII, claim(s) 22, drawn to methods of identifying an activity in an assay.
Group IX, claim(s) 23, drawn to a binding partner.

In addition to the 11 groups listed above, each group is further directed to 94 distinct embodiments corresponding to the 94 pairs of sequence identifiers for the 94 different polynucleotides and polypeptides encoded thereby. Each polynucleotide and encoded polypeptides lack unity of invention because they do not share the same special technical feature. A special technical feature means those features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. The special technical feature of each polynucleotide is the specific nucleic acid sequence of the polynucleotide molecule. Unity of invention is found between the polynucleotide, the polypeptide and the recombinant methods of use of the polynucleotide to make the polypeptide because claims to these categories of invention all share the special technical feature of the polynucleotide.

The inventions listed as Groups II-IX do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the inventions of Groups II and IX do not share the special technical feature of Group I, which is the nucleic acid sequence of the polynucleotide. Groups III-VIII are directed to additional methods, however, PCT Article 17(3)(a) does not provide for multiple products, processes of manufacture or uses which are claimed. Therefore, the first invention of the category first mentioned in the claims of the application and the first recited invention of each of the other categories related thereto is considered the main invention of the claims.